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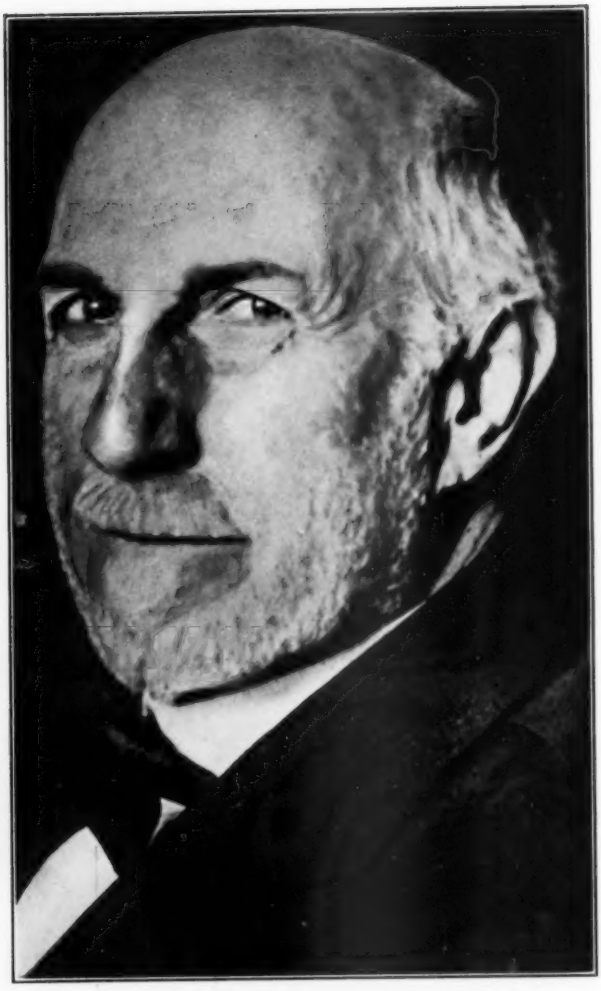

I. MINIS HAYS, A.B., A.M., M.D.

# I. Minis Hays, A.B., A.M., M.D.

With the death of Dr. I. Minis Hays on June 5 there passed a man whose name was connected with The American Journal of the Medical Sciences for over half a century.

Dr. Hays was born in Philadelphia on July 26, 1847, the son of Dr. Isaac Hays, himself for many years a prominent figure in Philadelphia medicine, and Editor of this Journal from 1833 to 1877. He was graduated from the University of Pennsylvania, receiving the degrees of A.B. (1866), M.D. (1868) and A.M. (1869). In the latter year he became Assistant Editor of the American Journal of the Medical Sciences, eventually succeeding his father to the editorship in 1878, a position which he held until 1890. He also edited the *Medical News* from 1878 to 1889. He wrote a number of articles in the domain of his specialty, ophthalmology, and edited the American edition of J. Soelberg Wells' *Treatise on the Diseases of the Eye*, which appeared in 1873.

As a member of the Association of American Physicians and of the College of Physicians of Philadelphia, he took an active part in the councils of his profession, and the College is indebted to him for twenty years of fruitful service as Chairman and Member of the Library Committee. In 1876 he was Secretary-General of the International Medical Congress which met in Philadelphia at the time of the Centennial.

But his interests extended beyond the sphere of medical activities, and it is as Secretary of the American Philosophical Society in the last twenty-eight years of his life that he will be especially remembered. For the space of a generation his was the guiding hand in the success of that organization. Particularly interested in its founder, Benjamin Franklin, he published a "Chronology of Benjamin Franklin" in 1904, of which a second edition appeared in 1913, and a "Calendar of the Franklin Papers" in 1907. The successful celebration in Philadelphia of the Franklin Bi-centenary in 1906 was largely due to Dr. Hays' efforts. Our knowledge of Franklin as a personality owes much to the historical researches of Dr. Hays.

The American Journal of the Medical Sciences takes this opportunity to pay tribute to his memory.

THE

# AMERICAN JOURNAL

# OF THE MEDICAL SCIENCES

JULY, 1925

## ORIGINAL ARTICLES.

### THE PREVENTION OF SIMPLE GOITER.

By J. C. Hathaway, M.B.,

MINNEAPOLIS, MINN.

(From the Laboratory of Physiological Chemistry, University of Minnesota.)

Simple, or endemic, goiter is one of the oldest maladies known to the world today. Mention of this occurrence may be found in the earliest medical literature. Extensive forms of exorcisms for goiter may be found in the Arthorva Veda, ancient Hindoo collection of writings, dated about 2000 B. C. A review of historical literature shows numerous publications on this subject at intervals up to the present time. It has been known in nearly all lands, and the sum total of its ravages throughout the ages has been enormous, yet it is only within recent years that methods for its prevention have been instituted. People living in maritime districts have had no cause to be concerned, while those living in inland districts have grown accustomed to regard it as a natural or normal state.

As statistics from various localities have revealed the existence of goiter from year to year, the truly astounding incidence of this disease has become manifest. In many of the goitrous districts more than half the people have large visible goiters. Goiter surveys showing the high incidence have been recognized as being essential in order to institute preventive measures, and are being conducted or are under contemplation in many places at the present time. Observation and surveys show that it is most prevalent during childhood, adolescence and during the period of pregnancy. Girls are affected about two to three times as frequently as boys.

The great geographical regions of endemic goiter, as is well known, are the Alpine regions of Switzerland, Italy, France, southern Germany and southern Austria; the Himalayan districts of India, southwestern China and eastern Mongolia; the Andes region of South America; the Great Lakes Basin, and the Cascade Mountain regions of Oregon, Washington and British Columbia, in this continent. A great many regions are known which may be classed as mildly and moderately goitrous. Nearly every country in the world has some districts which may fall into one of the latter classes.

Recently the situation has come more and more into the public eye. Papers on various phases of goiter are common in scientific and pseudoscientific literature and are not infrequent in the periodicals and newspapers of the day. The time is now ripe for the institution of extensive preventive measures in all the involved areas.

**Incidence.** While simple goiter may develop sporadically in almost any locality, as it did during one of Captain Cook's voyages, its strongholds have been in plateaus and mountain districts as in contradistinction to seacoast countries. Hirsch, in his publication on "The Historical and Geographical Relations of Goiter," in 1860, outlined these areas. As early as 1874 Baillarger, of the French Commission, estimated that there were 500,000 cases in France alone. A little later Kocher's statistics showed that 80 per cent of the school children of Berne were goitrous. Recently, in 1918, the health commissioner of the Canton of St. Gall showed the goiter incidence among school children to be 87.6 per cent. Klinger[17] states that 100 per cent of the school children are goitrous in some of the schools of Zürich, where he is carrying out methods of goiter prevention.

Schittenhelm and Weichardt[31] estimate the incidence of goiter in southern Bavaria as being 77 to 89 per cent of the total population. In Italy, from 1859 to 1864, 3 per cent of conscripts were excused from service because of this affliction. In Switzerland 12,207 men were exempted from military duty for this cause from 1875 to 1881. In 1912 McCarrison[20] reported 4869 cases in the district of Monghyr and 3142 cases in Bhagalpur in India, both of which districts lie in the Himalayan Mountains. He estimated that 20 per cent of the people in the Gilgit district (population, 70,000) had goiter. In the goitrous regions of Europe the percentage is even higher, as is shown above. In the United States a great many surveys have been recently made and statistics come pouring in. The following examples, which are all very recent, give an insight into the situation in all of the great goitrous regions of this country. Kerr[13] reported the examination of 21,182 recruits at Camp Lewis, Washington, and found 21 per cent having large and well-developed goiters. Smith[34] reports the examination of 65,507 men represent-

ing fifteen different central and western states at Jefferson Barracks, Missouri, with an incidence of 1.63 per cent showing large goiters. Hall[9] found 18 per cent enlargements in 2086 men (average age twenty years, five months) and 31 per cent of 1253 women (average age nineteen years, three months) at the University of Washington. Levin[18] examined 1783 unselected persons in two townships in the Great Lakes goiter belt (Houghton County, Mich.) and found 1146 goiters. Olsen and Clark[26] found 58 per cent of 4061 school children in thirteen localities in Minnesota to have goiters. In Montana[28] 13,937 school children were examined and 22 per cent found to have goiter. Olin[27] reports 47 per cent in 31,612 school children examined in Michigan. Marine and Kimball[25] examined nearly 10,000 school girls in Akron, Ohio, and found 56 per cent to have goiters. A recent survey in St. Paul,[30] Minn., showed 60 per cent thyroid enlargements in 582 high school pupils and 4615 grade school children examined. Clark[5] examined 13,836 school children in eleven counties of West Virginia and found about 9 per cent incidence; 6432 children in nine Virginia counties showed 12.7 per cent according to the same writer.

All of these statistics merely give an indication of the enormous degree of prevalence of this disease. Detailed surveys are now in progress in many of the goitrous regions, an instance of which is Utah, where Wallace is just completing the examination of over 100,000 children. This information is of the greatest value, as it is the basis for all successful measures of goiter prevention.

**Etiology.** Simple goiter has been associated with water as the etiological factor as far back as the history of goiter goes. According to Barton,[1] the American Indians were convinced of this relation. The natives of central Africa made this association (Livingston) as also did Hippocrates in his writings. The history of goiter is marked with numerous theories as to the causative factor; however, no one at the present time who has studied the situation considers goiter an idiopathic enlargement of the thyroid. A great many men have worked upon this problem during the last century, and a definite cause has been found for the immediate, if not for the remote, factor causing endemic goiter.

McCarrison[20] has done a large amount of work in an endeavor to find the causative factor, and believes it to be due to a waterborne infection, possibly a bacterium of the colon group. A few other workers, notably Shepherd[32] in his 1918 report on the occurrence of goiter in Canada, inclines to this view. However, in his more recent articles, McCarrison[20] attempts to reconcile his view with those who consider goiter a deficiency disease.

It has been said that the chemical constituents and also the bacterial content of drinking water in any locality are largely influenced by the nature of the soil and underlying rock strata. Goiter is more prevalent in the regions underlaid by the Silurian,

Carboniferous and Permian systems; while those of eruptive or crystalline rocks of the Archean groups, the sediment of Jurassic, Cretaceous and post-Tertiary seas, as well as fresh water deposits, are comparatively free from affection. Just how much influence this has upon the etiology of goiter is difficult to state.

Iodin starvation is now considered to be the immediate cause of simple goiter. Chatin,[4] a French chemist, first demonstrated this about 1850. He analyzed the water, food, air and soil of goitrous and nongoitrous regions, finding the goitrous areas to be low in iodin and the nongoitrous high. He advanced the hypothesis that goiter was due to a deficiency of iodin. The Commission appointed by the Paris Academy of Science to examine Chatin's work supported his analyses, but would not accept his conclusions concerning goiter, as it was impossible for them to attribute any virtue to $\frac{1}{400}$ mg. of any substance. However, his conclusions in general are accepted today.

Since Chatin's work several investigators have corroborated the facts by extensive analyses. Recently von Fellenberg,[36] and his collaborators in Switzerland, and McClendon and Hathaway[23] in this country, using more accurate methods and making many determinations, have demonstrated beyond a doubt that simple goiter is due to an insufficient quantity of iodin in food and drinking water. They have shown that food from nongoitrous regions may contain from 100 to 200 per cent more iodin than the same food from goitrous regions and that nongoitrous waters may contain as much as 20,000 times as much iodin as goitrous waters. They have also demonstrated experimentally the approximate amount of iodin that must be consumed daily to prevent the occurrence of goiter. The results of both of these groups of investigators are about the same and both come to about the same conclusions. Olin[27] and his collaborators, in making detailed surveys of the Michigan water supplies, are of the same opinion.

Baumann,[2] in 1896, demonstrated that the active principle of the thyroid contained iodin and indicated its relation to metabolism. In 1916 Kendall[12] definitely determined this substance as tri-iodo-indol-propionic acid and showed that it contained about 65 per cent iodin. He also demonstrated by animal experimentation its physiological action, and that its physiological action is proportional to its iodin content. Further animal experimentation, largely by Marine and Lenhart,[24] has shown that any substance substituted for iodin, destroys the physiological action of thyroxin, the thyroid hormone. It has also been proved histologically that glandular hypoplasia of the thyroid is due to a deficiency of iodin, and that if the content is maintained at or above 0.1 per cent no anatomical changes occur.

The most excellent work of Marine and Kimball[25] in this country, and the researches of Hunziker,[10, 11] Eggenberger[7] and more recently

Klinger,[17] in Switzerland, have shown absolutely that iodin in small quantities will prevent, and in larger quantities cure, simple goiter. Their striking results will be reviewed later in discussing methods of prevention.

What further evidence is necessary to establish the fact that this disease is due to iodin starvation?

**Methods of Prevention.** Iodin preparations have been unwittingly used as a goiter cure for centuries. Burnt sponge was used as a treatment by the Chinese over four thousand years ago and is also reported to have been used by the ancient Greeks. Dumas and Coindet,[6] in 1820, used iodin in the treatment of goiter, and from that time until about 1896 it was practically the only treatment used. Since Baumann's work in 1896, and the research of other men since that time, knowledge concerning the chemistry of the thyroid has become much better known and more definite methods of treatment have been instituted.

Up to the year 1917 no preventive measures of any extent had been instituted anywhere. Several physicians in private practice had advocated measures before this time, but the credit for the beginning of practical application of preventive methods to a large extent goes almost entirely to Marine and Kimball.[14, 15, 16] Marine and Lenhart[24] laid the foundation for this when they produced definite and convincing evidence that thyroid hyperplasia (goiter) could be prevented in animals by the administration of small amounts of iodin as sodium iodid.

(1) Marine and Kimball[25] gave prophylactic iodin to about 10,000 girls for at least one school term, these observations extending over a period of four years. They watched about 4000 for a period of from two to four years, during which time approximately one-half took enough iodin to saturate the thyroid twice a year, in the spring and fall. The other half took no iodin. They state that "Among those who took iodin as directed, who were normal when the administration was started, not one developed goiter, while among those who did not take iodin 27.6 per cent developed goiter. Moreover, among those who had goiters and took iodin systematically, in more than 60 per cent the thyroid gland returned to normal size; while among those who did not take iodin, in comparatively very few did the thyroid gland show any tendency to decrease in size." They first used 2 gm. of sodium iodid over a period of two weeks and repeated this dose twice yearly. They have changed their methods from time to time, and now advocate giving 10 mg. weekly throughout the school year in the form of chocolate-coated tablets of iodin in organic form.

Klinger[17] reports similar but even more striking results in three cantons of Switzerland. Muggio, using the same method throughout the districts of Sondrio, Italy, has had extremely good results. Contrary to medical opinion, these researches reveal the startling

fact that no cases of hyperthyroidism have resulted in any of those who have received prophylaxis, while mild iodism has occurred in less than 0.5 per cent.

This method of prevention would undoubtedly be the ideal one if it were not for the expense, the large amount of work necessary to put it into successful practice and the fact that it does not reach the pregnant woman. It is my belief that a cheaper, simpler and more universally useful method has been devised, at least for cities and those villages which have their own water supply, namely, the addition of an iodid to the city water supply.

The applicability and merits of different methods will be considered later.

2. The inhalation of air containing iodin, secured by suspending a bottle of tincture of iodin, has been advocated by Werth.[37] De Quervain, of the Swiss Goiter Commission, maintains that this method has not given any definite result. It has been argued that with this method the dose cannot be regulated, and that it is altogether too uncertain and impractical.

3. It has been suggested by Chatin, Sloan, Hirschfelder and others, that the admixture of small amounts of sodium iodid with common table salt could be made to suffice for iodin therapy, and such salt has been placed on the market as a commercial product in certain goitrous areas. If this were to be used on an extensive scale, all of the salt in the country would have to be so treated, as a person is at liberty to take his salt from any source. This would not be practical, as only a small part of salt sold is used for human consumption. Furthermore, von Fellenberg has shown that a large proportion of sodium iodid added to salt is lost in storage and must be added at least 100 per cent in excess to make sure the salt will contain the required amount. However, if the iodid is added in large enough amounts, such a preparation is undoubtedly of great value and could be used to advantage where other forms of iodin prophylaxis are not to be had, as, for instance, in country districts.

4. Eradication of goiter by a dietary regime has been suggested and advocated by certain men. Forbes and Beegle, McClendon and Hathaway[23] in this country, and von Fellenberg[36] in Switzerland, have shown that in goitrous regions iodin is present only in relatively very small amounts in nuts, fresh fruit, leafy vegetables, unrefined cereals and certain animal products (especially butter) and practically not at all in refined foods, particularly grains and some animal products. The only foods that would be of value in the prevention of goiter would be sea food (which has by far the largest iodin content of all foods) and nuts, butter fat, fruit, leafy vegetables, unrefined cereals and animal products from nongoitrous regions. Turrentine[35] strongly advocates the use of kelp which, as is well known, has a high percentage of iodin, and states that it

makes a very palatable food or may be taken in tablet form. It is undoubtedly true that if the diet of all the people could be amended to include these imported foods goiter could be controlled, but the time necessary to educate the public, together with the present prohibitive cost of preservation and transportation of such articles of diet, make such a proposition untenable. It is, however, at the present time a helpful adjuvant to the other methods which may be used, and in time might become more prominent as conditions change.

5. The addition of iodin to the water supply of a city which has been found to be high in goiter is one of the more recent methods of combating the situation, and shows promise of being the most efficient. McClendon and Hathaway[23] made analyses of water from a great many cities and localities, both goitrous and non-goitrous, and have come to the conclusion that about 1 part of sodium iodid in 100,000,000 parts of water would be sufficient to prevent goiter. One-tenth of a pound per 1,000,000 gallons would be ample. With such a method in operation, the taking of prophylactic iodin would not be left to the caprices of the individual or take the time of numerous doctors and school nurses. Everyone, particularly the school child and pregnant mother, would be insured of a sufficient supply of iodin. It is the simplest method yet devised, and should prove to be the most rapid and effective method in controlling goiter.

The water supplies of Rochester, N. Y.,[3] and Sault Ste. Marie, Mich., are now being treated with sodium iodid, with very good results. The details of adding the iodid are simple, the salt being added to the supply reservoir. Several cities in Minnesota (Minneapolis, St. Paul, Duluth and Virginia) are contemplating the use of this method, the popularity of which is increasing.

The arguments which have been used to discourage the treating of water supplies with sodium iodid are:

1. Such a procedure would give the water a bad taste. Some city waters have many times this amount of iodin and the water has no bad taste. More than a million times the necessary amount may be added without giving the water a detectable taste. Therefore, this objection should not obtain.

2. Some have opposed this on the grounds that it is medication, and therefore undesirable. This cannot be considered medication, as it is only supplying a deficiency and protecting against disease. If it is wrong to prevent goiter, why is it not wrong to spend enormous amounts each year in the sedimentation, filtration and chlorin treatment of water to protect against typhoid fever, tuberculosis and other water-borne diseases?

3. It has been said that this would be "poisoning" the water. Such an idea is, of course, ridiculous when the relatively minute quantity of iodid used is considered. Moreover, the water of some

cities on the western coast contains thirty times as much iodin as has been advocated for prophylaxis, and the possibility of their water being "poisoned" has never been contemplated by those living in these cities.

4. Some men feel that the treatment of the individual would be better. If the physicians of the country and the laity could all be educated as to the necessity of prophylactic iodin, this would undoubtedly be the better, although vastly more expensive, course to follow. However, such education would be a large problem, requiring many years to fulfil, and at the best the results would be uncertain. Furthermore, it would necessitate a large amount of work on the part of the public health officials in making sure that proper iodin prophylaxis was used in all places where it was a necessity, and such a procedure would entail enormous expense.

5. Some medical men have voiced the opinion that such a measure would have a deleterious effect on exophthalmic goiter. The results at Rochester, N. Y., do not show any evidence of this. The use of other methods of prophylaxis both here and abroad, where much larger doses have been in vogue, shows that not in a single instance has this occurred. Moreover, Plummer, at the Mayo Clinic, who probably has the largest series of exophthalmic goiter cases on record, has been using iodin in the treatment of these cases for some time, and reports excellent results.

6. It has been contended that the addition of iodin to the water supply is wasteful, and therefore expensive. It is probably true that less than 1 per cent of the water in a city is used for drinking purposes. Since this is true, why pay large sums yearly in purifying water for drinking purposes, over 99 per cent of which is wasted? Yet, that is what we do. In the one case the removal of pathogenic bacteria prevents water-borne disease, while in the other, the addition of the iodid prevents goiter. Is it not just as imperative that we spend small amounts to prevent one disease as to spend much larger amounts to prevent others?

The addition of sodium iodid is really inexpensive. The city of Rochester, N. Y., with a population of about 315,000, spends $3000 per year, or less than 1 cent a year per person. This certainly is not so expensive a procedure but that we can afford to waste a certain amount. Moreover, some of the iodin wasted is used in watering stock and irrigating food plants and is thus returned to the human system.

It has been claimed that the use of iodin in tablet form is the most economical. Whereas sodium iodid in the water supply costs about 1 cent per year per person, druggists sell these tablets at the rate of about $1.50 per year per person, although a special wholesale rate at the small price of about 50 cents per year per person may be made to schools. We can afford to waste a little iodid from our water supplies and thereby save considerable money.

7. The economists have brought forth the theory that wholesale treating of water supplies would soon deplete the world's source of iodin. The world's supply of iodin is so huge that we cannot conceive of it. McClendon has calculated that the sea contains about 66,000,000,000 tons. This iodin is extracted at a rapid rate by sea weed and industries could easily be developed to utilize it.

**Conclusions.** *Eradication of Goiter.* A method which would control the goiter situation should consist of the following:

1. Detailed surveys should be made of all localities where goiter is suspected. This is the basis for all successful methods of goiter prevention.

2. The institution of treatment with sodium iodid of the water supplies of all cities and towns which prove to be goitrous.

3. Small villages not having a common water supply, and rural communities, must have iodin supplied either by the use of iodized table salt or by iodin tablets of some kind.

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## PURPURA HEMORRHAGICA (THROMBOCYTOPENIC PURPURA) WITH REPORT OF A CASE WITH SPLENECTOMY.

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Sir William Osler[1] referred to purpura as "That obscure and interesting manifestation of which we know so much and at the

same time so little." Since Osler made this reference much has been done to properly classify conditions accompanied by purpura. The present-day conception of the classification and diagnosis of primary purpuric disease still resembles, however, the state of the conception a number of generations ago of intermittent fever. Knowing the exact etiology of malaria as we now do, we can project the probable fact that patients suffering from intermittent fever of pyogenic origin were grouped together with patients infested with the plasmodium of malaria and considered as having an identical disease. Atypical cases of malaria without intermittent fever no doubt escaped true classification.

Aplastic anemia, purpura hemorrhagica, and acute myelogenous leukemia may show clinical signs and symptoms of very similar character—an acute downward fatal course, hemorrhages from mucous membranes, purpuric eruption, reduction of blood platelets, prolonged bleeding time and profound anemia. In the majority of cases final classification into one of the three groups is possible. But borderline cases occur where the exact diagnosis must remain in doubt, even in the presence of collected evidence from history, physical examination, clinical laboratory data, and postmortem examination of tissues. No one at the present time is able to say, definitely, whether these three diseases are or are not related. E. Frank, the distinguished German hematologist, believed primary aplastic anemia and purpura hemorrhagica to be the same disease. Others equally distinguished are of a different opinion.

In the year 1731, Werlhof[2] separated purpura hemorrhagica from the general group of purpuric diseases. Hayem[3] in 1889 emphasized the observation, published by Denys[4] two years previously, that the blood platelets were present in markedly decreased number in a case reported by Denys. Since that time nosologists have shifted their point of view from the manifestation, *purpura*, to the manifestation, *reduction of blood platelets* in their attempt to arrive at a proper classification. This has led to the coining of a number of new names for the condition which no doubt will be discarded in turn, when the final etiology of the entity is arrived at. The disease probably occurs in mild form without the manifestation, reduced blood platelets, and without purpuric spots.

Wright made the observation in 1906 that blood platelets are derived from the pseudopodia of the megakaryocytes of the bone marrow. No one has successfully disputed this finding since that time and gradually it has been accepted. Much remains unknown, however, concerning the origin and physiology of these peculiar bodies.

In 1915 E. Frank[5] arrived at the conclusion that the blood platelets are *always* reduced in purpura hemorrhagica and proposed the name "essential thrombopenia." In 1920 Eppinger[6] suggested that essential thrombocytopenia was a better term as directly pointing

to reduction of the platelet cells rather than the substance thrombin. Hayem noted the extraordinary fact that there is an absence of clot retraction in primary purpura hemorrhagica. Duke[8] in 1912 emphasized the prolonged bleeding time in the presence of a normal coagulation time in this disease.

Theories of pathogenesis of primary purpura hemorrhagica have been many and interesting. Certain French writers[9] held that disturbances in hepatic function were primarily at fault. Grenet's work[10] indicated that a toxic action on the central nervous system was the primary factor. The theory of infection has had many advocates. Giffin and Holloway[42] state: "There is a growing conviction that it (purpura) is usually secondary to localized infection and that in some way chemical toxins are formed as the result of bacterial action which affect the vascular tissue." They suggest that the process is not due to the direct action of a bacterium or its products, but to a secondary abortive substance originally designed to protect, the process probably being linked with protein intoxication.

Primary changes in the walls of the capillaries have been demonstrated in experimental purpura. In 1914 Ledingham[49] produced purpura with hemorrhagic symptoms by injecting animals with antiblood-platelet serum. Bedson[11] concluded from observations on experimental purpura in 1922 that the two main factors concerned in the production of hemorrhages in purpura are: (1) Toxic action on the endothelium of bloodvessels; (2) removal of platelets from the circulation.

Recently Bedson[43] has investigated the effect of splenectomy upon the blood platelets in experimental purpura. He states that splenectomy in guinea pigs gave rise to a great increase in the number of blood platelets in the blood stream. Blood platelets reached their highest level in ten to fourteen days and declined to normal in three or four weeks. Bedson concludes that splenectomy cannot be relied on to give any but temporary relief in the treatment of purpura hemorrhagica. This is especially important in view of the recent literature on splenectomy as a curative measure in purpura hemorrhagica.

Frank[14] formulated a theory in 1915 that hemorrhages in primary purpura were due to an inhibitory action of the spleen on the bone marrow causing a reduction of the number of blood platelets in the circulation. Kaznelson[16] agreed with Frank that the spleen was concerned in the reduction of blood platelets in hemorrhagic purpura but thought its action was a destructive one on the platelets after formation rather than an inhibition of proper formation. Brill and Rosenthal[13, 41] have suggested that the entire so-called reticulo-endothelial system is concerned in the reduction of the number of blood platelets, the reticulo-endothelial tissue of the liver, lymph nodes and elsewhere participating as well as that of the spleen.

The treatment of primary purpura hemorrhagica has included

efforts by local and general styptic drugs to combat hemorrhages, injection of serum, injection of foreign protein, roentgen rays over the spleen and bone marrow, and recently the operation of splenectomy. In 1916 Kaznelson[16] reported brilliant results following splenectomy in a case of thrombocytopenic purpura hemorrhagica. Since that time approximately 50 patients[13, 42] have been splenectomized for this condition in various parts of the world. The majority of these reports are confirmatory of the value of this procedure.

**Case Report.**—E. M., aged eighteen years, a school girl, was admitted to the Pennsylvania Hospital, Philadelphia, on November 4, 1924, on the service of Dr. Charles F. Mitchell. Her chief complaint was bleeding from the vagina and gums. For the past ten months she had felt generally weak and had been told by relatives that she was pale. For the past two months she had been bleeding at intervals small amounts from the gums; and for the past five weeks she had been bleeding from the vagina. About a month before admission a large number of purpuric spots appeared on the skin. These lasted for a long time but disappeared. Her appetite was poor. Her bowels were constipated. She had had repeated attacks of sore throat during the past few years.

*Physical Examination.* The patient is a well-developed, well-nourished girl, but very pale and seems to be extremely anemic. Bleeding from the gums is the only positive finding about the head. There is no adenopathy. Examination of the lungs shows nothing abnormal. The heart is negative except for a soft systolic murmur at the apex. The spleen and liver are not felt and there are no masses or areas of tenderness. She is bleeding and passing clots from the vagina.

On account of the possibility of incomplete abortion, a dilatation and curettage was done on the day of admission. Blood clots were evacuated, but the patient continued to bleed. There was no evidence on examination of curettings of an abortion.

Shortly after this a diagnosis was made of purpura hemorrhagica.

Dr. George W. Norris made the following note on consultation on November 12: "Blood-pressure 117/55. Small pea-sized pale bluish-red petechial spots on left groin. Several brownish spots on back, smaller and may have had similar origin. Constriction of brachial vessels by blood-pressure cuff for about two minutes sufficient to cut off circulation has not produced petechia. Several petechial spots over right inner lower biceps region. Pain and tenderness right lower abdomen. Spleen not felt, not enlarged to percussion. Lungs clear. Heart not enlarged. Soft low pitched systolic murmur at apex of heart. Liver not felt except in epigastric notch. I believe this is a case of purpura hemorrhagica and in view of recent literature, splenectomy might be considered."

*Course of Disease.* On November 12: Transfusion—300 cc whole blood, direct method. The patient continued to bleed. The

transfusion improved her general condition but she did not stop bleeding from vagina. The bleeding from the gums has practically stopped.

November 15: Transfusion two hours before operation of 475 cc of whole blood. The spleen was removed. It was found to be somewhat enlarged and adherent to the diaphragm. The tail of the pancreas was also adherent near the hilus of the spleen. There was very little oozing. The patient's pulse became quite rapid during the operation, reaching 170 per minute but remained of fair volume. She reacted well from the operation.

She was considered to be in such good condition after coming out of ether that a postoperative transfusion was not done.

November 17: Given 35 cc of whole blood intramuscularly. The patient has continued to bleed from the vagina since operation about the same as before. Bleeding from the gums has ceased.

November 19: Transfusion of 400 cc of blood.

The patient's general condition improved after each transfusion but bleeding continued from the vagina.

November 21: The uterus packed with gauze soaked in thromboplastin.

November 21: Several small purpuric spots have appeared under the left breast.

November 22: Bleeding has stopped from vagina since packing.

November 22: 700 cc whole blood transfused.

November 23: Her temperature has risen to 106° F. (rectal), pulse 120. No bleeding from uterus.

November 24: Her temperature rose this P.M. to 105° F. (rectal); pulse rate 120. There is a systolic murmur at the apex; the abdomen is soft, with no tender points, or masses. The operative incision is in excellent condition. She has been incontinent all day, passing bowel movements and urine in bed frequently.

November 28: Great numbers of purpuric spots have appeared over the whole body. The tourniquet test is positive. There is no bleeding from the uterus, and most of the packing has been removed. The patient is extremely anemic and the effect of blood transfusion lasts but a day or two.

November 29: Transfusion of 400 cc of citrated blood did not produce a reaction and the patient died shortly after.

*Laboratory Work.* The Wassermann test was negative. Analyses of urine showed albumin present, varying from a trace to a heavy cloud, with no sugar or casts. Both aërobic and anaërobic blood cultures were made. On November 12 blood cultures were negative. On November 28 a rod-shaped organism was seen in a Wright's stain of the blood. Blood cultures taken immediately showed the Bacillus fecalis alkaligines in both aërobic and anaërobic cultures. It may be interesting here to note that this organism was found also postmortem in cultures from the vena cava.

Clotting time on November 7 was seven minutes. On November

17 it was four minutes; November 28, four minutes. Oxidase stains made both before and after operation showed the abnormal mononuclear cells present to belong to the myeloblastic series. The red blood cells both before and after operation showed polychromatophilia, some poikilocytosis and anisocytosis and occasional stippling.

Examination of the feces was negative except for a strong reaction for occult blood. There was no frank bleeding from the lower bowel.

Bleeding time on November 7 was twenty minutes; on November 15, thirty minutes; on November 17, four minutes; on November 27, twenty minutes.

Clot retraction was absent both before and after operation. The blood when allowed to remain several days in the ice box showed no retraction of clot.

BLOOD COUNTS.

| Date. | Red blood cells, millions. | Hemoglobin, per cent. |
|---|---|---|
| November 4 | 3,000 | 35 |
| November 7 | 1,160 | 25 |
| November 11 | 0,945 | 25 |
| November 16 | 1,270 | 25 |
| November 17 | 1,035 | 25 |
| November 18 | 1,043 | 25 |
| November 19 | 0,786 | 20 |
| November 21 | 0,730 | 20 |
| November 24 | 1,650 | |
| November 26 | 1,480 | 25 |
| November 28 | 1,100 | 20 |

WHITE BLOOD CELL COUNTS.

| | | Differential count in per cent. | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Date. | Total count, per c.mm. | Poly. | Lymphо. | L. M. | Tr. | Eos. | Myelocytes. | Nucleated reds per c.mm. |
| November 4 | 9,600 | 31 | 32 | 2 | 4 | 0 | 31 | 0 |
| November 7 | 5,200 | 33 | 28 | 2 | 1 | 0 | 36 | Occasional |
| November 10 | 9,400 | 27 | 8 | 4 | 1 | 0 | 54 | 0 |
| November 17 | 40,000 | 56 | 4 | 2 | 3 | 0 | 35 | 45,000 |
| November 18 | 37,000 | 50 | 7 | 1 | 2 | 0 | 40 | 43,000 |
| November 19 | 54,000 | 43 | 7 | 1 | 0 | 0 | 49 | 36,000 |
| November 20 | 34,000 | 52 | 1 | 0 | 2 | 0 | 45 | Many |
| November 21 | 20,400 | 45 | 10 | 2 | 1 | 0 | 42 | 47,000 |
| November 22 | 23,236 | 46 | 9 | 0 | 0 | 0 | 45 | 39,564 |
| November 23 | 55,000 | 42 | 3 | 0 | 0 | 0 | 55 | 105,000 |
| November 24 | 24,950 | 66 | 3 | 2 | 1 | 0 | 28 | 80,850 |
| November 26 | 36,000 | 90 | 2 | 0 | 0 | 0 | 8 | 24,000 |
| November 28 | 53,000 | 62 | 2 | 0 | 0 | 0 | 36 | 7,200 |

BLOOD PLATELET COUNTS.

| Date. | Per c.mm. |
|---|---|
| November 11 | 40,000 |
| November 14 | 30,000 |
| November 16 | 80,000 |
| November 17 | 70,000 |
| November 18 | 70,000 |
| November 19 | 64,000 |
| November 24 | 90,000 |
| November 26 | 130,000 |

*Examination of Spleen Removed at Operation.* The spleen is moderately enlarged, weighing 190 gm. Its surface is smooth and glistening. The capsule does not appear to be thickened. The cut surface is uniform in color. There are no gross nodules or areas of localized involvement. The pulp is of a brick red color and lies even with the cut surface. The reticulum grossly shows no apparent increase in amount.

Microscopic sections show no thickening of the capsule. The trabeculæ are prominent and distinct but there is no evidence of increased amount of fibrous tissue in the spleen. The germinal centers are distinct. The blood spaces are filled with cells having the morphological appearance of myeloblasts and myelocytes. The arrangement or lack of arrangement of these cells suggests that they are transient cells. There is no evidence of the uniform hyperplasia of cells *in situ* with destruction of architecture so characteristic of the myeloid hyperplasia of myelogenous leukemia. The lymphocytes and lymphoblastic cells of the germinal centers show no evident deviation from normal morphology. No blood platelets can be distinguished.

*Postmortem Findings.* (Dr. J. R. Paul.) The body is that of a well-developed and well-nourished young Italian girl. There is a very marked pallor of the skin and mucous membranes. Scattered over the chest and abdomen are showers of purpuric and ecchymotic spots. These are present over the breasts, upper abdomen and anterior surface of the arms. The legs are more or less free from these spots although there are two present over the femoral triangle on both sides. There is a recent "T"-shaped surgical incision in the left middle quadrant of the abdomen (both arms measuring about 15 cm. in length). It is fairly well healed but the edges are hemorrhagic and serum oozes from it.

The examination is confined to the surgical incision.

Peritoneal Cavity: On opening the peritoneal cavity it is found to be free from blood, although parietal and visceral peritoneum are studded here and there with tiny ecchymotic spots. An extremely interesting condition is encountered in that there is a well-developed sac of peritoneum situated on the left side of the peritoneal cavity, the orifice of which is opposite to Treitz's fossa. Fully two-thirds of the small bowel is loosely enclosed in this sac. As the duodenum and jejunum emerge from Treitz's fossa they enter this sac and the gut in this region is small, extremely pale and collapsed. Its contents are small in quantity and pale pink. In striking contrast is the appearance of the small gut as it emerges from the sac. It becomes distended, the walls are extremely dark and the contents dark red. There is no evidence of incarceration or strangulation. The colon is somewhat dilated throughout. All of the mesenteric lymph nodes are tremendously enlarged and edematous, some are cherry red in color, others are pale red, varying

in size from that of a pea to an olive. This includes the glands in the mesentery, about the celiac axis and along the spinal column. In contrast the glands in the pubic region and mediastinum are not enlarged. In the region of the splenic flexure (spleen removed) there is a large collection of broken down blood. Most of it seems to be retroperitoneal in location and situated about the tail of the pancreas.

The lungs and heart are examined through the diaphragm.

Heart: Definite cardiac hypertrophy is present.

Lungs: Pulmonary edema, mild in extent is present in both lower lobes.

Stomach, Duodenum, Pancreas: No gross changes noted.

Intestines: As noted above.

Liver: The liver is of normal size and appearance except for pallor.

Adrenals: The adrenals are small and pale orange in color. No hemorrhages.

Kidneys: Both kidneys present the same picture. They are quite large. The surfaces are smooth and pale. On section the cortex is found to be quite thick, extremely pale and the renal architecture poorly defined. The picture is that either of extreme anemia, or acute parenchymatous degeneration and infiltration of white cells.

Pelvic Organs: The uterus is small and of normal shape and size. It is dark red in color. The walls and cervix are soft. On exposing the uterine cavity a dark semigangrenous endometritis is encountered. Both ovaries are enlarged. The tubes are normal. The bladder is normal.

*Autopsy Sections.* Pancreas: The islands appear to be somewhat hypertrophied. The capillaries and other blood spaces contain blood showing many myeloblastic cells and nucleated red cells. No other noteworthy changes.

Liver: The capsule shows no changes. The liver cells appear shrunken. Some contain fat droplets. The capillaries are dilated and contain blood with a high percentage of myeloblastic cells. There is an occasional small area of perivascular exudation of cells of the same type seen in the blood stream. These resemble more an inflammatory reaction than the infiltrative areas usually encountered in leukemia.

Adrenals: Section is not remarkable. Bloodvessels contain myeloblastic cells.

Kidneys: Sections show very few changes except cloudy swelling of the tubular epithelium. The glomeruli, bloodvessels and interstitial tissue are not particularly abnormal in appearance. There are no focal collections of cells.

Small Intestine from Hernial Sac: The changes are not striking.

Several dilated lymphatics are present in the submucosa. The bloodvessels are dilated with myeloid cells.

Uterus: Sections show erosion of the mucosa with congestion and vacuolization of the epithelial cells of the glandular acini. The uterine veins are dilated and in places filled with plugs of blood and fibrin containing large numbers of polymorphonuclear and myeloblastic cells. There is no definite infiltration of interstitial structures with myeloblastic cells.

Mesenteric Lymph Node: The capsule is not thickened. The architecture of the node is largely preserved. There is marked edema. The marginal and septal sinuses are filled with red blood cells, nucleated red cells, myeloblasts and lymphocytes with a few large phagocytic cells enclosing red cells, mononuclear cells and debris. The pulp shows the same picture as that detailed above except for more abundant fixed cells of lymphocytic type. The uniform hypertrophy of abnormal cells seen in the leukemias is not present.

Bone Marrow: The bone marrow is quite cellular. There is no evidence of fatty infiltration or replacement. The cells are largely myeloblasts, erythroblasts and occasionally megakaryocytes, with some red blood cells containing no nuclei. Occasional phagocytic cells are seen containing ingested debris and cells. The impression one gets is that the mother cells of both the red cells and the polymorphonuclear cells are quite active and hyperplastic.

**Summary of Findings.** An eighteen year old girl was admitted to the hospital with a history of purpuric spots on the skin two months previously. Purpuric spots were present during stay in hospital and constriction of arm with blood-pressure cuff produced purpuric spots. For two months before admission she had been bleeding small amounts from the gums. For five weeks before admission she bled more or less continuously from the vagina. She developed extreme anemia but her general nutrition remained good and there was very little emaciation. None of the superficial lymph nodes were enlarged. The spleen was not particularly enlarged. There were no signs of cardiac or pulmonary disease or evidence of localized infection.

Bleeding time was prolonged. There was marked reduction of blood platelets. Coagulation time was normal. Clot retraction was absent. Anemia was profound. Before blood transfusion 3 counts of white blood cells ranged from 5200 to 9600; a differential count showed myeloblasts and myelocytes present. These were interpreted as a symptomatic myeloblastic stimulation from strain of repeated hemorrhages on bone marrow.

A splenectomy was done after preliminary blood transfusion.

Following splenectomy the patient ceased to bleed from gums. Vaginal bleeding continued until the uterine cavity was packed. After operation repeated transfusion of whole blood was done. The

effect of raising the hemoglobin and red cell content of the blood was only temporary, though there was no gross evidence of red cell destruction such as jaundice.

The patient died apparently of anemia and exhaustion despite repeated transfusions. After splenectomy there was an enormous increase of nucleated red cells with a large number of leukocytes of myeloblastic origin.

**Discussion.** The question of the proper diagnosis of this case presents some difficulty even in the presence of fairly detailed clinical history, laboratory results and postmortem findings. The patient presented the cardinal signs and symptoms of thrombocytopenic purpura: (1) Purpuric eruption; (2) hemorrhages from gums and vagina; (3) marked anemia; (4) prostration; (5) absence of a definitely localized area of disease to account for the condition; (6) prolonged bleeding time; (7) normal coagulation time; (8) marked diminution of blood platelets; (9) absence of clot retraction.

The unusual feature, however, was the presence of myelocytes and promyelocytes in fairly large relative proportion.

Ordway and Gorham[48] state: "A diagnosis of acute myelogenous leukemia in order to be above criticism must be substantiated by proof of the following points: (1) An aleukemic or subleukemic stage; (2) an acute downward course with death usually in from one to four months; (3) the characteristic picture of myeloblasts and myelocytes with transition forms between the two; (4) typical gross and histological findings in the liver, spleen, bone marrow and lymph glands; (5) specific proof of myeloid elements by enzyme reactions (oxidase stains)."

In regard to Item 4 they say: "A slight myeloid change is not sufficient proof. It must be a marked transformation since mild proliferation of myeloid tissue is not uncommon in severe anemias. The possibility of error in failing to insist upon this point is well illustrated by Naegeli."[47]

Myeloid changes in the tissues of the case under discussion were not striking. The picture was not at all typical of the usual myeloid hyperplasia of leukemia. The myelocytes and myeloblasts present in the kidney, spleen, lymph nodes and liver were largely contained in bloodvessels and blood spaces. The uniform hyperplasia of myeloblasts in the enlarged lymph nodes with destruction of architecture so characteristic of the leukemias was entirely lacking. Stimulation myelocytosis in severe anemias, especially acute and subacute types of severe anemias, is a comparatively common finding. Examples might be multiplied of this type of myelocytosis in severe anemias with subsequent complete recovery of the patient.

We have felt, therefore, that it is impossible to classify the case as acute myelogenous leukemia and feel that the case was one of

severe essential thrombocytopenic purpura with marked stimulation myelocytosis.

Consideration of the question of why the patient failed to recover after splenectomy is of speculative interest and may afford some practical points. Transfusion of blood was not done immediately after the operation. Brill and Rosenthal consider that blood transfusion should immediately precede and follow the operation. It was not immediately done after operation by us because of the apparently good condition of the patient and because we considered the transfusion immediately preceding the operation to have been sufficient.

After operation the patient stopped bleeding from the gums, but continued to bleed from the vagina until the uterus was packed. It is possible that local measures to control vaginal bleeding should have been taken earlier. We hesitated to do this because of the danger of infection and because we hoped day after day that bleeding from the uterus would stop.

The theory of Brill and Rosenthal[41] that the entire reticuloendothelial system is involved in platelet destruction, that in the lymph nodes, liver, and elsewhere as well as the spleen, calls up the speculation as to whether in very severe cases such as the one under discussion, sufficient of the offending system is not removed by splenectomy to stop the process.

The finding of the jejunal hernia is of interest. Its significance is not apparent. While the patient had no clinical signs of intestinal obstruction the well known intensity of reaction from the absorption of toxic products from an obstruction to the higher portions of the bowel makes this fact of the hernia of enough speculative interest to be mentioned in a discussion of the case. It is possible that the immediate origin of the organism isolated from the blood (Bacillus alkaligines) was from the partially imprisoned loop of small bowel, and that the retrogression following the temporary postoperative improvement may have been due to absorption of toxins from this area. Certainly the microscopic appearance of the mesenteric lymph node lends support to this view.

As we watched the blood picture from day to day we were struck by the profound struggles of the bone marrow to replace red blood cells in the circulation, as witnessed by the enormous numbers of nucleated red blood cells. Lenoble[44] believed he had discovered a new form to which he gave the name of myeloid purpura. This was characterized by the presence of a considerable number of normoblasts in the circulating blood. In the acute stage of the disease the number varied between 165 and 1250 per c.mm. In 1 case he found 3000 per c.mm. Sometimes according to Lenoble, neutrophilic myelocytes and more rarely eosinophilic myelocytes are found in the blood during a myeloid reaction. Labbé and Ameuille[45] concluded from their study that there was nothing specific

in the myeloid reaction. It varied with the extent of the hemorrhage and disappeared when bleeding ceased.

The number of nucleated red blood cells in our case after splenectomy reached the enormous number of 105,000 per c.mm. We have not found in the literature any case approaching this figure. Before splenectomy was done there were only a few nucleated red cells although the anemia was almost as profound at times before operation as after it. It certainly seemed that removal of the spleen profoundly stimulated the formation of young red blood cells either directly or indirectly. Examination of the blood count chart shows that the blood platelets were increased over the former figure after the removal of the spleen. There was a temporary reduction of the bleeding time. Bleeding from the gums ceased immediately after the operation. The total number of leukocytes was increased. This is usual after splenectomy. For a time the patient appeared to be improved clinically.

Transfusion of whole blood in our case appeared to be a useless measure to control bleeding. It was of value in temporarily raising the content of red blood cells and hemoglobin in the circulation.

Operation was approached in the case of the patient here recorded with a certain degree of confidence, our feeling being that if the patient survived the operative procedure we might expect a cessation of her hemorrhagic symptoms. We were disappointed. The patient made a good recovery from a surgical viewpoint after the removal of the spleen and evidence of stimulation of the functions of the blood forming organs was evident after operation but this was not sufficient for recovery.

We are aware of the fact that the final diagnosis in this case is somewhat problematical and that some may be inclined to consider it acute myelogenous leukemia with purpuric features. We have no desire to be dogmatic in our diagnosis. The bulk of the evidence appears to us to place the case as one of primary purpura hemorrhagica with stimulation myelocytosis. But we are quite willing to recognize that we may have the clinical entity hemorrhagic purpura merging in various degrees into the equally poorly limited field of leukemia.

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## WASSERMANN-FAST SYPHILITICS TREATED WITH BISMUTH.

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We propose in this article to show that bismuth has a real therapeutic value in reducing the "positiveness" of the Wassermann reaction or rendering it negative in the socalled "Wassermann-fast" patients. The term "Wassermann-fast" is restricted to those patients who have had one or more routine courses of arsphenamin and mercury without any appreciable reduction in the blood Was-

sermann. After a review of the literature up to this time we have been unable to find a series of such cases reported. It may be stated that each patient in this series had a negative lumbar puncture prior to bismuth therapy. Each patient has had a urinalysis before the institution of bismuth injections and subsequent monthly analyses during their treatment.

The epoch making work of Sazerac and Levaditi[1] in 1921 on the treatment of rabbit syphilis with bismuth heralded a new drug to the armamentarium of the therapy of syphilis. Soon after came the reports of Fournier and Guenot[2] on their clinical observations of 200 human syphilitics in all stages treated by this new antisyphilitic agent.

Syphilographers in all countries began experimenting with the various bismuth preparations. We soon learned that bismuth would cause cicatrization of the chancre and the disappearance of the concomitant adenopathy; regression of all secondary and tertiary manifestations with almost the same rapidity as the arsenical preparations; the Wassermann test in the preserologic period could be controlled and, if positive, could be reduced or rendered negative.

We also have learned that patients reacting unfavorably to arsphenamin will tolerate bismuth without the slightest difficulty. There are cases on record of patients whose symptoms have actively recurred while under arsenical treatment only to clear up with bismuth. Other cases have been reported in which both mucous membrane and cutaneous lesions have failed to disappear after vigorous arsenical and mercurial treatment, but responded quickly and favorably to bismuth.

One of us, who first used bismuth in this country on human syphilis, noticed that a few patients who were Wassermann-fast following intensive arsenical and mercurial treatment soon reacted with negative test when bismuth was used. Other writers about this time reported an occasional case responding similarly. We, therefore, decided to treat a series of patients with bismuth who were Wassermann-fast subsequent to intensive arsenical and mercurial treatment in order to ascertain whether the occasional cases reported were mere coincidences or whether we were dealing with a drug which had a definite therapeutic action in influencing the Wassermann reaction.

We selected our patients for this work in the order in which they came to the clinic. Each patient has had a complete physical, neurological, blood Wassermann, spinal fluid serology and urinalysis done before the beginning of bismuth therapy. All of these patients treated may be regarded as purely asymptomatic syphilitics with only a positive blood Wassermann test. No patient was selected who showed any trace of a positive spinal fluid in either cells, globulin, Wassermann test or colloidal gold.

BLOOD WASSERMANN TEST

| Case No. | Number of doses of intravenous arsphenamin. | Number of mercurial injections. | Date. | Before treatment, blood Wassermann test. | After first course of 16 bismuth injections. | After second course of 16 bismuth injections. | After third course of 16 bismuth injections. | Albumin in urine. | Remarks. |
|---|---|---|---|---|---|---|---|---|---|
| 399 | 67 | 60 | 1920–1923 | ++++ | ± | − | − | Negative | Feels fine. |
| 353 | 51 | 41 | 1921–1923 | ++++ | +++ | +++ | ++ | Negative | |
| 272 | 59 | 71 | 1920–1923 | ++++ | ++++ | + | + | Negative | Says "he never felt better." |
| 105 | 50 | 63 | 1920–1923 | ++++ | ± | ++ | .... | Negative | |
| 450 | 31 | 28 | 1922–1924 | ++++ | +++ | +++ | (+) negative | Negative | During first course of bismuth legs weak; arms painful. Later preferred bismuth to any other form of treatment. |
| 367 | 31 | 31 | 1922–1923 | +++ | − | − | + | Negative | |
| 1182 | 30 | 20 | 1916–1923 | ++++ | ± | ± | .... | Negative | |
| 240 | 34 | 41 | 1922–1923 | ++++ | + | ± | − | Negative | Feels fine. |
| 196 | 47 | 42 | 1922–1923 | ++++ | ± | .... | .... | Negative | |
| 92 | 32 | 38 | 1922–1924 | ++++ | ++ | ± | +++ | Negative | |
| 1320 | 39 Mixed treatment—pills, etc. Private treatment for three years. | 20 | 1924 | ++++ | − | +++ | ++ | .... | First course of bismuth reduced blood to complete negative for first time in five years. |
| 115 | 27 | 30 | 1922–1923 | +++ | − | − | .... | Negative | |
| 328 | 32 | 18 | 1921–1924 | ++++ | − | − | .... | Negative | |
| 291 | 63 | 75 | 1918–1923 | ++++ | ± | Stopped in − midst of this course | .... | Negative | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | 1919–1923 | ++ | − | − | .... | Negative | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| this course | | | | | | | | | |
| 939 | 26 | 20 | 1919–1923 | ++ | − | − | .... | Negative | |
| 270 | 46 | 82 | .... | + | ± | ± | .... | Trace after first course | Pain in back—sleepy—tired. |
| 254 | 37 | 40 | 1922–1923 | ++++ | ++++ | ++++ | ++++ | Faint trace after first course, cleared up later | |
| 122 | 42 | 60 | 1922–1923 | ++++ | ++++ | ++++ | Incomplete | Negative | |
| 635 | 52 | 77 | 1919–1923 | ++++ | ++++ | ++++ | ++++ chol. ± alc. | Faint trace after second course—negtive third | |
| 502 | 17 | 20 | 1922–1923 | ++++ | After 7 bismuth injections W. R. ++++ | .... | .... | Negative | After first injection developed urticaria arms and legs. After second injection developed maculo-papular rash. Pains in legs. Bismuth stopped after seventh injection. |
| 253 | 32 | 50 | 1922–1923 | ++++ | ++++ | .... | ..... | Negative | |
| 1154 | 15 | 17 | 1923–1924 | ++++ | ++++ | ++ | .... | Negative | |
| 551 | 19 | 17 | 1922–1923 | ++++ | +++ | .... | .... | Negative | |
| 507 | 27 | 16 | 1922–1923 | ++++ | ++++ | ++ | .... | Negative | |
| 107 | 29 | 20 | 1919–1923 | ++++ | ++++ | + | .... | .... | Difficulty with arsphenamin and mercury. Faint trace albumin in urine after fifth injection. Off of treatment for two weeks. Urine showed few fine granular casts. Stopped treatment for two months. Began treatment again but only a faint trace showed. |

**Summary of Findings.** There were 25 patients treated in our series all of whom have been under bismuth therapy for one year. Each patient has received bismuth intramuscularly twice weekly until 16 injections have been given. This constitutes one course after which all treatment was suspended for one month at the end of which time a blood Wassermann was made.

In each patient, as the chart shows, the blood Wassermann was 4+ with the exception of 4 patients, 2 of whom were 3+, 1, 2+, and 1, 1+, respectively.

After the first course of bismuth therapy, 11 patients out of 25 (44 per cent) gave a negative or plus-minus Wassermann reaction; 9 were unchanged (36 per cent) and 5 were either slightly reduced or reduced to 1+ (20 per cent). In other words in 64 per cent of the cases the Wassermann reaction was improved or rendered negative by bismuth after remaining unchanged for one or more years of arsphenamin and mercurial therapy.

Following the second course the serology was further improved. However, only 21 patients continued their treatment. Of this number 14 were serologically improved or remained negative (66⅔ per cent); 5 were unchanged from their previous status (23.8 per cent) and 2 had reverted from plus-minus to 2+ and negative to 3+ respectively (9.5 per cent). There was a further improvement after this course over the first course of 22⅔ per cent; opposed to 9.5 per cent relapse.

Only 11 patients finished the third course. Of this number 7 remained negative or were further improved (63.6 per cent); 1 remained unchanged (9.09 per cent) and 2 reverted, 1 from negative to 1+ and 1 from plus-minus to 3+ (18.1 per cent). One course was incomplete.

The average percentage of improvement or negative serology after three full courses of bismuth was 64.7. The percentage of unchanged Wassermann reactions from the original after three full courses was 22.96. The percentage of reversions after the second and third courses was 13.8.

It has been stated at various times that bismuth was prone to produce an albuminuria. A glance at the chart does not bear out these statements. We observed a faint trace in only 4 cases which cleared up before the third course except in 1 patient in whom the trace persisted throughout.

It might be appropriate here to say that in only 1 patient did we observe any cutaneous eruption which cleared up quickly after withdrawal of all treatment. We had no cases of stomatitis nor any untoward symptoms excepting an occasional tenderness where the injections were made. However, these were not more painful than mercury and some patients preferred bismuth to mercury. We frequently saw gingival pigmentation but this was of no moment.

**Conclusion.** We believe that bismuth has a real and lasting place in treating Wassermann-fast syphilitics. In view of the fact that the Wassermann has remained negative for nearly a year or more in a large percentage of our patients, we believe that the permanency of this reduction cannot be denied. However, a greater length of time is required, free from all treatment, before we can definitely affirm this permanency of the reaction.

1. Bismuth should be given in all Wassermann-fast syphilitics.
2. Albuminuria is not produced more frequently with bismuth than with other antisyphilitic agents.
3. No untoward effects are met with in bismuth therapy when properly administered.

We desire to thank Dr. D. D. Stetson for permitting us to carry out this work in his service. To Dr. Randal Hoyt we express our thanks for performing the lumbar punctures and making the neurological examinations. We express thanks to Dr. D. S. Jessup for the urinalyses and to Dr. Frederick Fox for doing the serology. Both alcoholic and cholesterinized antigens as well as water-bath and ice-box fixations were done on all Wassermanns. The preparation used in this work was potassium and sodium tartrobismuthate.

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## THE WASSERMANN REACTION IN THE BLOOD AND SPINAL FLUID OF PARETIC NEUROSYPHILIS.

### With the Presentation of the Results in One Hundred and Sixty-six Consecutive Hospitalized Cases.

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The purposes of this paper are: (1) To discuss the frequency of a positive Wassermann reaction in the blood as compared to

a positive reaction in the spinal fluid in paretic neurosyphilis, and (2) to discuss the frequency of a negative spinal fluid in paretic neurosyphilis.

**I. Findings in the Present Series.** The findings of the Wassermann reaction in a series of 166 consecutive cases of general paralysis are presented, taken from the records of the Boston Psychopathic Hospital in 1919, with the permission of the Director, the late Dr. E. E. Southard.* Symptomatological analysis of these 166 cases has been presented elsewhere.[1]

In this series of 166 cases there were 3 in which the Wassermann was not done; in 143 cases it was performed on both the blood and spinal fluid; in 11 cases only on the blood; in 9 cases only on the spinal fluid. The results follow:

Blood Wassermann performed in 154 cases, with 137 positive reactions.

Spinal fluid Wassermann performed in 152 cases, with 143 positive reactions. Hence, in 154 cases clinically diagnosed general paralysis 90.1 per cent showed a positive blood Wassermann reaction, while 94.8 per cent of 152 cases gave a positive spinal fluid reaction, indicating in this series that the spinal fluid Wassermann reaction is positive more frequently than the blood Wassermann.

Comparison of the serum and spinal fluid results in the 143 cases in which blood and spinal fluid Wassermann tests were performed is made in Table I.

TABLE I.

| Number of cases. | Blood serum. | Spinal fluid. | Per cent. |
|---|---|---|---|
| 124 | Positive | Positive | 86.7 |
| 5 | Positive | Negative | 3.4 |
| 11 | Negative | Positive | 7.6 |
| 3 | Negative | Negative | 2.2 |

From these data it may be noted that 9.8 per cent of 143 cases had a negative Wassermann test on the blood and 5.6 per cent a negative test on the spinal fluid.

**II. Frequence of Positive Serum and Spinal Fluid Reactions.** There is considerable disagreement at the present time on the frequency of the occurrence of a positive Wassermann reaction in the blood in general paralysis as compared with its frequence in the spinal fluid. Many workers have found the spinal fluid to give a higher percentage of positive reactions than the serum, as has occurred in the present series detailed above. Boyd[2] states that it is always positive in the fluid, and also states that it is very rare for the reaction to be positive in the serum and negative in the fluid. Eskuchen[3] has recently published his results in 346 cases of syphilis of the central nervous system, in which he found

* The permission of the present director, Dr. C. Macfie Campbell, was also secured for the publication of these data.

97 cases which gave a negative blood reaction and a positive spinal fluid reaction. Of 72 cases of general paralysis, 5.5 per cent gave a negative blood and a positive spinal fluid Wassermann reaction. Kafka,[4] in a series of 124 cases of general paralysis, found nearly 20 per cent which showed a positive spinal fluid and a negative serum Wassermann reaction. Eichelberg[5] obtained positive tests in every spinal fluid of patients with general paralysis. Marie, Levaditi and Yamanouchi[6] found 93 per cent positive reactions in the spinal fluids of 30 cases of general paralysis. Nonne,[7] as quoted by Levinson, holds that if sufficient fluid is used the test is positive in all cases of syphilis of the central nervous system. Haguenau[8] states that practically all authors admit that the Wassermann reaction is nearly always positive in the spinal fluid of general paralysis, and quotes a large number of workers to support this statement. Sicard[9] has contended for nearly two decades that the spinal fluid in this condition is always positive, and still maintains this view. Sabatini[10] states that even with treatment in his cases the fluid remains constantly and irreducibly positive. Cestan and Riser[11] in 40 cases found positive reactions in the fluid in every instance, although it was necessary to use very large quantities of the fluid in some. Smith and Candler,[12] in England, found 92.1 per cent positive Wassermann reactions in the fluid of 64 paretics. Rizzo[13] believes the result of the Wassermann test of the spinal fluid is always of greater value than the result of the blood test. Darling and Newcomb[14] found a positive Wassermann reaction in the spinal fluid of all paretics; while a positive reaction in the blood seemed the rule, repeated negative findings could not exclude the diagnosis of paresis. Marie and Levaditi[15] found 73 per cent of 39 cases gave a positive reaction in the fluid compared to 59 per cent of 30 cases in the blood. And to cite other findings: Miller, Brush, Hammers and Felton[16] found 98 per cent of 130 cases with a positive spinal fluid Wassermann reaction; Noguchi and Moore[17] report 73 per cent in 60 cases; Wassermann and Plaut[18] found 88 per cent in 41 cases; Morgenroth and Stertz,[19] 100 per cent in 8 cases; Noguchi, Rosanoff and Wisemann,[46] 87.5 per cent in 56 cases. Fuchs[20] gives a series of 56 cases of latent syphilis showing no signs of nervous disease, but all with changes in the spinal fluid. Of a total of 131 cases examined, 29 per cent had negative blood Wassermann reactions, although all had changes of some kind in their spinal fluids. Fildes, Parnell and Maitland[21] found the cerebrospinal fluid was abnormal in a series of 624 cases of syphilis in all stages, in which there was no clinical sign or symptom of nervous disease. Twenty-nine cases had over 100 cells per 1 c.mm. and 9 had over 300. Moleen[22] cites several cases without signs or symptoms showing changes in the spinal fluid, including a positive Wassermann test.

TABLE II.—WORKERS FINDING POSITIVE SPINAL FLUID WASSERMANN TEST MORE CONSTANT THAN POSITIVE SERUM WASSERMANN.

| Author. | | Findings. |
|---|---|---|
| Wassermann and Plaut[18] | 1906 | 41 cases with 88 per cent positive fluids. |
| Marie and Levaditi[15] | 1907 | 39 cases, 73 per cent positive fluids and 59 per cent positive serums. |
| Morgenroth and Stertz[19] | 1907 | 8 cases, all positive fluids. |
| Eichelberg[5] | 1908 | 100 per cent positive spinal fluids. |
| Marie, Levaditi and Yamanouchi[6] | 1908 | 30 cases, 93 per cent positive fluids. |
| Noguchi and Moore[17] | 1909 | 60 cases, 73 per cent positive fluids. |
| Smith and Candler[12] | 1909 | 64 cases, 92.1 per cent positive fluids. |
| Noguchi, Rosenoff and Wiseman[16] | 1910 | 56 cases, 87.5 per cent positive fluids. |
| Darling and Newcomb[14] | 1916 | Positive fluid in all cases and serum usually positive. |
| Sabatini[10] | 1918 | Spinal fluid always positive. |
| Boyd[2] | 1920 | Fluid always positive; rarely positive serum with negative fluid. |
| Haguenau[8] | 1920 | "Nearly always positive in fluid." |
| Kafka[4] | 1920 | 20 per cent with positive fluids and negative serum. |
| Miller, Brush, Hammers, Felton[16] | 1920 | 98 per cent of 130 cases with positive fluids. |
| Sicard[9] | 1920 | "Fluids always positive." |
| Cestan and Riser[11] | 1922 | 40 cases, all fluids positive. |
| Fuchs[20] | 1922 | 29 per cent of 131 cases of central nervous system syphilis with negative serum Wassermann. |
| Rizzo[13] | 1922 | "Fluid test of more value than serum test." |
| Eskuchen[3] | 1923 | 72 cases, 5.5 per cent with positive fluid and negative serum. |
| Nonne[7] | 1923 | 100 per cent of fluids positive with sufficient amount used. |

On the other hand, there are many writers who hold that the serum usually presents a higher percentage of positive reactions than the spinal fluid. Boas[23] has reported 100 per cent positive serum reactions in a series of 243 cases, while he obtained only 94 per cent positive spinal fluid reactions in 201 cases. He points out that the majority of German workers find the serum more frequently positive, while the majority of French workers have found the fluid more constantly positive, and cites several on each side of the question. Craig[24] states that in paresis the Wassermann test is positive in the blood in nearly 100 per cent of the cases, and if sufficient spinal fluid is used it is positive in practically 100 per cent. Edel[25] found 100 per cent positive reactions in the serum in 62 cases. Plaut[26] found in 1420 cases none with negative blood and positive spinal fluid Wassermann reactions, although he noted 8 cases in which the reaction was negative in both the spinal fluid and the serum. Nonne and Holzmann[27] found 100 per cent positive reactions in the serum and nearly so in the fluid. Stertz[28] found 95 per cent of the spinal fluids gave a positive reaction, but asserted that the serum generally gives better results than the fluid. Marinescu[29] found 94 per cent of 35 cases gave positive Wassermann tests in the serum. Raviart, Breton and Petit[30]

record 93 per cent of 72 cases with positive reactions in the serum, and Lesser[31] found 100 per cent of 62 cases. There are workers who have found the Wassermann test positive in both the blood serum and the spinal fluid in practically all cases (Craig,[24] Plaut,[26] Nonne and Holzmann,[27] McIntosh and Feldes[32]).

TABLE III.—WORKERS FINDING POSITIVE SERUM WASSERMANN TEST MORE CONSTANT THAN POSITIVE SPINAL FLUID WASSERMANN.

| Author. | | Findings. |
|---|---|---|
| Edel[25] | 1908 | 62 cases, 100 per cent positive serums. |
| Lesser[31] | 1908 | 62 cases, 100 per cent positive serum. |
| Raviart, Breton and Petit[30] | 1908 | 72 cases, 93 per cent positive serum. |
| Stertz[28] | 1908 | 95 per cent positive fluid, and serum with better results than fluid. |
| Marinescu[29] | 1909 | 94 per cent of 35 cases with positive serum; fluids less. |
| Nonne and Holzmann[27] | 1910 | 100 per cent positive serum and nearly so in fluid. |
| Plaut[26] | 1920 | 1050 cases, 42 cases with negative fluid and positive serum. |
| Craig[24] | 1921 | 100 per cent of serum positive and nearly 100 per cent of fluids. |
| Boas[33] | 1922 | 243 cases, 100 per cent positive serum and 94 per cent positive fluids. |

**III. Occurrence of Negative Wassermann Test in the Spinal Fluid in Paretic Neurosyphilis.** From the above, it appears that a large number of workers have found a negative Wassermann test in the cerebrospinal fluid in some cases of general paralysis, varying from 1 to 2 up to as high as 27 per cent of the cases, the great majority being less than 10 per cent. It is generally recognized (Boyd,[2] Rizzo,[13] Craig,[24] etc.) that the Wassermann reaction in the fluid in general paralysis is stronger and obtained with a less amount of the fluid than in any other syphilitic disease of the central nervous system, and this fact has been suggested as a point in differential diagnosis. However, apparently it is negative in certain cases, as for example in our own series there were 5.6 per cent of 143 cases which had a negative reaction in the fluid.

Despite the fact that in the past, as has been cited, many workers have reported a negative Wassermann reaction in a small but rather constant percentage of active cases of general paralysis, there is a variance of opinion as to whether the spinal fluid may be normal in the presence of active central nervous system syphilis. It is recognized that the Wassermann reaction may be negative while the fluid may show other signs of activity. However, Solomon and Klauder[33] state that the only type of neurosyphilis in which it is generally recognized that the spinal fluid may be negative is that in which the disease process, as far as the central nervous system is concerned, affects almost solely the bloodvessels—thrombosis, hemorrhage, cerebral aneurysm and arteritis obliterans. Hoaglund and Prioleau[34] report a large occipital gumma with

practically no changes in the spinal fluid and a negative Wassermann test.

Nonne[35] has classified into five groups the negative spinal fluids in neurosyphilitics:

1. The fluid is normal from the beginning, a rudimentary process.
2. The fluid begins as pathological but becomes normal, this being the case in healed syphilitic disease of the central nervous system.
3. The fluid shows improvement over its former condition but is still not entirely normal. In this condition the disease process is improved.
4. The fluid is still pathological as it was earlier, but the clinical picture has remained stationary.
5. The fluid remains pathological as it was formerly, with an increase in the disease process.

Solomon and Klauder[33] have added to this classification a sixth group in which the fluid may have no pathologic changes or very mild ones, and the disease be active and progressive, and cite as evidence active cases of tabes, cerebral gumma, cerebral syphilis of the type causing nerve palsies, Erb's syphilitic spastic paraplegia, syphilitic epilepsy, syphilitic paranoia and syphilitic dementia, all with negative spinal fluids. They agree that in many instances in which the evidence of a syphilitic nervous involvement is shown by the physical signs and the fluid is normal these signs present evidence of a former activity which has been halted. Wynn[36] has reported 2 cases of paresis in which the spinal fluid changes after treatment suggested improvement while there was no clinical evidences of improvement and there have been many references to similar observations in connection with the various recent treatment innovations. Fordyce and Rosen[37] have pointed out that the classical symptoms of tabes dorsalis may occur with a negative Wassermann reaction in spinal fluid and blood, and Thaysen[38] presents a series of 30 cases of tabes dorsalis developing with negative serum Wassermann tests, 7 cases of which also had negative spinal fluid Wassermann tests, and 5 of these 7 cases gave a definite history of syphilis. Dreyfus[39] has pointed out that 35 to 40 per cent of tertiary syphilitics with isolated pupillary abnormalities have negative Wassermann reactions in the spinal fluid, and the fluid remains negative after provocative arsphenamin injections. Wüllenweber[40] also found that a certain number of a series of 28 cases of syphilis showing only pupillary changes have a negative spinal fluid Wassermann test, and believes the prognosis better in these cases than in those where the fluid shows alterations. In Plaut's series of 1050 cases[26] of general paralysis in which both the serum and spinal fluid Wassermann tests had been done, there were 42 cases in which the fluid was negative, although the serum was positive. Boas[23] found 12 cases in a series of 201

of general paralysis (6 per cent) with a negative Wassermann test in the spinal fluid. In a series of 204 cases of neurosyphilis Worster-Drought, Fry and Lynch[41] found 35 in which the clinical evidence of neurosyphilis was definite with the cerebrospinal fluid yielding a negative Wassermann reaction but a positive colloidal-gold curve. Of these 7 were "taboparesis," 3 with a positive Wassermann test in the blood serum, and 4 with a negative serum Wassermann. As has been mentioned, Stertz,[28] Marinescu,[29] Nonne,[35] Smith and Candler[12] and others have found a certain percentage of negative Wassermann reactions in the spinal fluid of active cases of general paresis. Targowla[42] concluded from his study of the fluid in paresis that none of the various tests were specific, but must be taken together with the clinical picture to establish the diagnosis. We may safely state that there is a large group of workers who believe that the spinal fluid may have a negative Wassermann reaction in paretic neurosyphilis.

However, there are still many workers who agree with Ernest Jones,[43] when he summed up the knowledge concerning the serodiagnosis of general paralysis in 1909, by stating that "A positive reaction in the cerebrospinal fluid is strongly indicative of a general paralysis, and a negative reaction is less strongly, but unquestionably indicative of its absence." Even more will agree with his statement that "A positive reaction in the blood of a suspected case of general paralysis is of some value in support of the diagnosis, and a negative reaction is of much greater value in excluding such a diagnosis." Boyd[2] states very positively that the Wassermann reaction in the spinal fluid of general paralytics is always positive, whereas it is negative in at least 70 per cent of cases of cerebrospinal syphilis with 0.2 cc of fluid. Nonne[7] gives 100 per cent positive Wassermann reactions in the cerebrospinal fluid in general paralysis, tabes dorsalis and cerebrospinal syphilis if large quantities of the fluid are used. Craig[24] states that if 0.5 cc of fluid are used practically 98 per cent of cases of paresis will give a positive reaction in the spinal fluid, a result never found in any other condition of the central nervous system. Eichelberg[5] found 100 per cent positive reactions in the fluid. As has been mentioned before, Sicard[9] has long maintained that the fluid is always positive. Cestan and Riser[11] were able to obtain a positive reaction in the fluid in all of 40 cases, though in some it was necessary to use very large amounts of the fluid. Rizzo[13] goes so far as to state that a positive Wassermann reaction in the spinal fluid is the only sure index of a neurosyphilitic lesion.

Craig[24] holds that this wide variety of opinion is due to failure to use sufficient amount of fluid. He states that "because of the use of too small amounts of spinal fluid in making the Wassermann test, much of our data regarding the occurrence of a positive reaction in the various syphilitic infections of the central nervous

system are worthless." He gives credit to Hauptmann and Hossli[44] as "the first to insist upon the use of a large quantity of cerebrospinal fluid in applying the Wassermann reaction and their work changed entirely the prevalent conception of the comparative rarity of a positive reaction in diseases like tabes, and demonstrated that almost any syphilitic disease of the central nervous system would give a positive Wassermann reaction with these larger amounts of fluid." In his own experience he finds that if 0.5 cc of spinal fluid is used in paresis practically 98 per cent will give a positive reaction, while if smaller amounts be used the percentage of positive results will be found to decline to about 75 per cent, or 80 per cent when 0.2 cc is used. Boyd[2] has also found the principle true, that larger amounts of fluid frequently give positive reactions where smaller amounts give negative reactions. As has been cited, Cestan and Riser[11] obtained 100 per cent positive reactions in the fluids of 40 cases of general paralysis, although in some instances they used 5 to 6 cc of the fluid in making the test Hence there is strong evidence that most of the discrepancies which exist are due to failure to use sufficient amount of fluid in making the test. However, we believe that there is sufficient evidence from the work of reliable men that the spinal fluid may be entirely negative in the presence of active neurosyphilis, and that the Wassermann test may be negative in the spinal fluid in paretic neurosyphilis.

TABLE IV.—WORKERS NOTING 100 PER CENT POSITIVE SPINAL FLUID WASSERMANN REACTIONS IN PARETIC NEUROSYPHILIS.

| Author. | | Findings. |
|---|---|---|
| Eichelberg[5] | 1908 | 100 per cent of cases. |
| Darling and Newcomb[14] | 1916 | Positive in all cases. |
| Sabatini[10] | 1918 | Positive even after treatment. |
| Sicard[9] | 1918 | "Always positive." |
| Boyd[2] | 1920 | 100 per cent in paresis; 70 per cent in cerebrospinal syphilis. |
| Craig[24] | 1921 | "Practically 98 per cent" if sufficient fluid is used. |
| Cestan and Riser[11] | 1922 | 100 per cent positive in 40 cases. |
| Nonne[7] | 1923 | 100 per cent positive with sufficient fluid. |
| Rizzo[13] | 1923 | Positive Wassermann only sure index of syphilis. |

Another theoretical consideration regarding the occurrence of a positive and negative reaction with the Wassermann test in the fluid of syphilitics has been suggested by Eicke and Löwenberg,[45] who showed that after heating the fluid to 56° C. for half an hour and so inactivating it, weakly positive reactions became negative and other positive reactions became less strongly positive. Rizzo[13] has pointed out that fluids from neurosyphilitics which give a positive Wassermann reaction when active, and a negative reaction

when inactivated, give in both states a positive colloidal benzoin reaction; in other words, the results of the two reactions are not parallel, which is also borne out by the findings of Worster-Drought, Fry and Lynch,[41] cited above. Rizzo further states that the general paralytic spinal fluid does not present this phenomenon of thermolability; the intensity of the Wassermann reaction in the inactivated fluid of a general paralytic is the same or slightly less than that of the activated fluid and he considers this a differential diagnostic point.

**Summary.** 1. The majority of investigators have found the cerebrospinal fluid to give consistently a higher percentage of positive Wassermann reactions in paretic neurosyphilis than the blood serum, although many reliable workers have found a positive serum to be the more frequent.

2. In the present series in 154 cases clinically diagnosticated general paresis 137 cases (90.1 per cent) showed a positive blood serum Wassermann test; of 152 cases the spinal fluid gave a positive Wassermann test in 143 (94.8 per cent).

3. In 143 cases both the serum and spinal fluid Wassermann tests were performed. Of this number both the spinal fluid and serum were positive in 124 cases (86.7 per cent); there were 5 cases with the blood positive and the spinal fluid negative (3.4 per cent); 11 cases with the blood negative and the spinal fluid positive (7.6 per cent); 3 cases with both the blood and spinal fluid negative (2.2 per cent).

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## CONDITIONS SIMULATING ACUTE LYMPHATIC LEUKEMIA (INFECTIOUS MONONUCLEOSIS. TUBERCULOSIS).

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The early diagnosis of acute lymphatic leukemia rests largely on the number, the relative proportions and the character of the white cells in the blood. It is important to recognize that other conditions may show blood changes so similar as to deceive the most expert observers. It is the purpose of this paper to record and discuss two such instances.

**Case Reports.** Case I.—**Acute Infectious Mononucleosis with Vincent's Angina.** A white unmarried woman, aged twenty-six years, whose previous health and habits had been excellent and who had not been subject to upper respiratory infections, was taken ill on March 27, 1924, with a sore throat accompanied by headache, body pains, mild fever and prostration. On the fourth day of her illness, when I first saw her, the pharynx was congested, the tonsils being small and in no way abnormal. Two tender nodes the size of a pea were felt below the jaw on the left side, and there were a few shot-like, insensitive inguinal nodes. Otherwise, there was no enlargement of the superficial nodes. The heart and lungs were negative, neither the liver nor the spleen could be felt. The patient did not appear acutely ill. Her pulse and respiration were normal, and the temperature by mouth was 99.4° F. The symptoms suggested a mild pharyngitis. On the fourteenth day I was again called because she had not improved as expected. The patient had felt unable to go out and had spent a larger part of the time in bed. Her throat and neck had remained sore and she had continued having a little fever, up to 100.6° F. by mouth. The throat appeared about the same but the cervical glands were a little larger and more tender.

The spleen had become palpable. The blood was examined to exclude malaria and showed an amazing change; 12,500 white cells with 86 per cent mononuclears (78 per cent large mononuclears and 8 per cent small lymphocytes). A well-known hematologist was asked to examine this blood and he reported 15,000 white cells with 83 per cent mononuclears (including 41.5 per cent large mononuclears and 31 per cent small lymphocytes). The majority of these cells were distinctly abnormal, the predominating type being somewhat larger than the larger lymphocytes with pale blue cytoplasm and oval lobulated or kidney-shaped nucleus which stained intensely. (Fig. 1.)

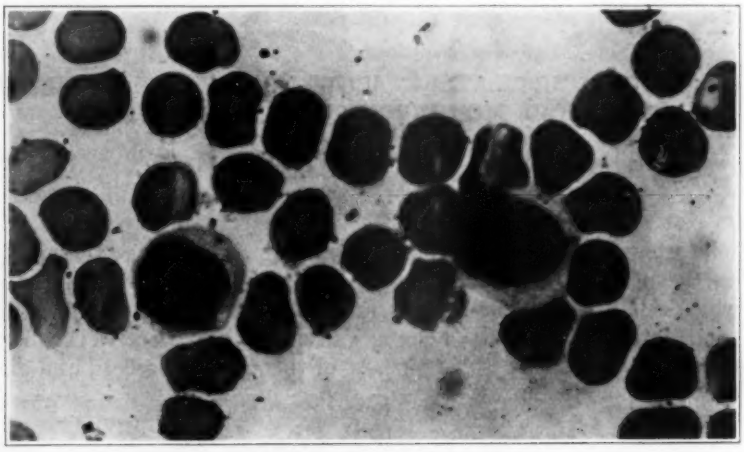

FIG. 1.—Type of cell found in Case I.

On April 14, the nineteenth day of her illness, the patient entered Roosevelt Hospital and two days later was seen by an eminent medical consultant who considered acute lymphatic leukemia the most probable diagnosis. In the mean time smears had been sent to Dr. B. M. Randolph of Washington, the patient's family physician, and referred by him to Dr. Hunter of the George Washington University Pathological Laboratory. I am indebted both to Dr. Hunter and Dr. Randolph for this and subsequent blood examinations. Dr. Hunter did not think the slide showed leukemia and he could not identify any cells of marrow origin. An oxidase stain done at the Roosevelt Hospital on April 19 also failed to reveal marrow cells.

Immediately after her admission to the hospital, the patient's throat began to get definitely worse and the temperature rose steadily to nearly 104° F. Within three days, on the twenty-second day of her illness, a membrane formed on both tonsils with the typical appearance of Vincent's angina, a diagnosis which the

laboratory fully confirmed. At the same time there was an increase in the size and number of the glands, more becoming tender on both sides of the neck and some also becoming palpable in both axillæ. Radiograph made at this time showed nothing abnormal in either heart or lungs. The urine also was normal. Following two applications of arsphenamin to the throat there was a rapid improvement; the throat lesions cleared up; the temperature fell and the spleen diminished in size so that it could no longer be felt. By April 20, the twenty-fifth day of her illness, the patient was convalescent except that the glandular enlargement and the blood changes persisted unchanged until April 27, when she returned to Washington. On May 9, the leukocytes had fallen to 6400 but there were still 58 per cent mononuclears. On February 18, 1925, a final blood count showed 7000 leukocytes with 28 per cent mononuclears, only 3 per cent of which were of the abnormal type described above. Dr. Randolph reports an uneventful recovery and complete return to vigorous health. Tonsillectomy was performed in June, 1924.

TABLE I. BLOOD FINDINGS IN CASE I.

| Date. | Hgb., per cent. | R. B. C. in millions. | W. B. C. in thousands. | Neut. | Bas. | Eosin. | Lympho. | Large mono. and transit. | Pre myelo.‡ | Türck cells. | Count by. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1924. | | | | | | | | | | | |
| April 9 | 75 | .. | 12.5 | 14 | ... | ... | 8 | 78 | .. | .. | Self |
| April 11 | 78 | 4.690 | 15.1 | 12.5 | 3.5 | 1.0 | 31 | 41.5 | .. | .. | Dr. Sondern |
| April 14 | 75 | 4.595 | 20.2 | 12 | 1 | 1 | 14* | 72 | .. | .. | Roosevelt Hospital |
| April 18 | 75 | .. | 15.6 | .. | Differential as above | | | | .. | .. | Roosevelt Hospital |
| April 23 | .. | .. | .. | 25 | ... | ... | 55 | 9 | 9 | 2 | Dr. Hunter |
| April 26 | .. | .. | .. | 12 | ... | ... | 48† | 40 | .. | .. | Self |
| May 2 | .. | .. | .. | 38 | ... | ... | 55 | 2 | 2 | 1 | Dr. Hunter |
| May 9 | 83 | 4.800 | 6.4 | 41 | ... | 1 | 52 | 4 | 2 | .. | Dr. Hunter |
| Aug. 13 | 80 | 4.500 | 7.5 | 52 | ... | 3 | 44 | 1 | .. | .. | Dr. Hunter |
| 1925. | | | | | | | | | | | |
| Feb. 18 | 85 | 4.350 | 7.0 | 68 | 1 | 3 | 25 | 3 | .. | .. | Dr. Hunter |

* In the proportion of 2 large to 12 small.
† In the proportion of 30 large to 18 small.
‡ On April 11 there were 8 per cent myelocytes and 2.5 per cent myeloblasts.

Acute infectious mononucleosis, glandular fever, or acute benign lymphoblastomatosis, of which the case just cited is an example, has aroused considerable interest in the past few years, because of epidemics, occurring chiefly in England, in which glandular swelling, sore throat and fever have been associated, in some cases, with a blood picture suggestive of leukemia. The first mention of an epidemic of glandular enlargement accompanied by fever was made by

E. Pfeiffer in 1889. This syndrome in the next few years was described quite generally under the term glandular fever, by Türck, West, Marchand, Cabot, Deussing and others. The most comprehensive reviews of the subject in recent years have been made by Tidy and Morley, who in 1921 brought the literature up to date, by Tidy and Daniel in 1923, and in this country by Longcope in 1922, Sprunt and Evans in 1920, Morse and Bloedorn and Houghton in 1921. Most of these authors believe in the identity of glandular fever and acute infectious mononucleosis.

The symptoms are mild fever and prostration lasting two to three weeks, a sore throat, without exudate on the tonsils, enlargement of the cervical glands regularly and of other superficial nodes occasionally, not infrequently a palpable spleen and often an increase of the leukocytes with a relative mononucleosis which may run as high as 34,000 white cells and 89 per cent mononuclears. (Longcope). The cytoplasm of these cells is greater in volume and more deeply staining than that of normal small lymphocytes. Their nuclei are irregular and frequently notched. Degenerating forms are absent in contrast to their frequency in acute lymphatic leukemia. With oxidase stain these cells do not show granules indicating marrow origin and hence are believed to be of lymphoid origin.

The cause of infectious mononucleosis is unknown. Some authors consider it a form of infection with the organism of Vincent, and the case here reported lends support to this view. Tarnow, in an extensive study of the blood of individuals suffering from a Vincent's throat, found that the mononuclear cells ranged from 5.6 per cent to 27.6 per cent. On the other hand many cases of Vincent's angina show nothing abnormal in the blood. It would be interesting to determine the reaction of the blood of animals infected with the Vincent's organisms, but unfortunately, the cultural characteristics of the spirillum makes this experimental work impractical. In one case reported by Sprunt and Evans, the patient showed a typical polymorphonuclear blood response to ordinary pyogenic infection a year after having an acute mononucleosis so the condition is not a peculiar individual response to ordinary infections. The prognosis of this condition is uniformly good.

Case II.—**Lymphocytosis with Tuberculosis.** A colored girl, aged sixteen years, was admitted to Roosevelt Hospital on May 21, 1920, had been suffering from pain in the upper abdomen for eight months. For two days previous to admission her throat had been sore. There were no other symptoms. On examination she was well nourished and did not appear very ill. There was an ordinary follicular tonsillitis. Throat cultures were negative for diphtheria. The cervical and axillary nodes could just be felt but were not tender. Examination of heart, lungs and abdomen revealed nothing abnormal. The blood pressure was 110 over 70. The urine on four exami-

nations showed specific gravity ranging from 1012 to 1028, a trace of albumin, a few hyaline casts once and no sugar. The stools contained a little blood on two occasions, but no ova or parasites could be found. Rectal and vaginal examinations were negative. Radiographic examination of the chest showed a large node at the left hilus but nothing else abnormal. The blood Wassermann and Widal tests were negative. No tubercle bacilli were found in the sputum.

The remarkable blood findings are shown in Table II.

TABLE II. BLOOD FINDINGS IN CASE II.

| Date. | Hgb., per cent. | R. B. C. in millions. | W. B. C. in thousands. | Mononuclear cells, per cent. |
|---|---|---|---|---|
| May 21 | 78 | 2.840 | 9.4 | 80 |
| May 25 | .. | .... | 11.2 | 87 |
| May 27 | .. | .... | 23.4 | 96 |
| May 28 | .. | .... | 34.8 | 96 |
| May 30 | .. | .... | 17.0 | 90 |
| June 1 | .. | .... | 34.0 | 96 |
| June 5 | .. | .... | 36.8 | 95 |
| June 7 | .. | .... | 29.9 | 95 |
| June 9 | .. | .... | 31.2 | 95 |
| June 13 | 22 | 1.144 | 8.6 | 96 |
| June 15 | 28 | 1.552 | 8.6 | 94 |
| June 17 | 24 | 1.212 | | |
| June 19 | .. | .... | 11.6 | 95 |
| June 21 | .. | .... | 23.8 | 97 |
| June 27 | .. | .... | 8.4 | 95 |

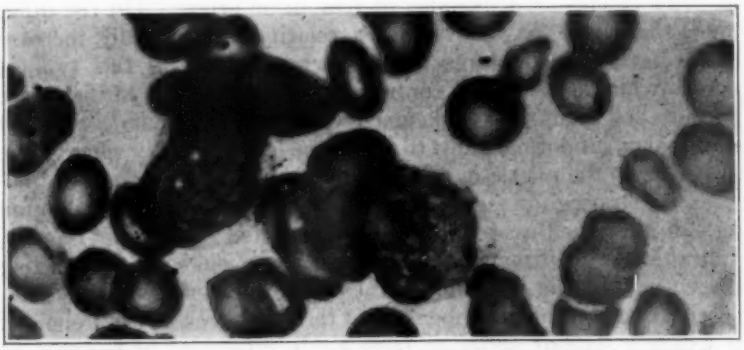

FIG. 2.—Type of cell found in Case II.

The mononuclear cells were mostly large with horseshoe nuclei and devoid of cytoplasmic granules (Fig. 2); nor could any of these be shown after oxidase staining. No nucleated red cells were ever found. The patient had a persistent and increasing temperature

and progressively lost flesh and strength. No other physical signs were found. She died on June 28, five weeks after admission. Three members of the attending staff concurred in the diagnosis of acute lymphatic leukemia. The autopsy showed tuberculous bronchopneumonia in the left upper lobe with tuberculosis of the tracheal and bronchial lymph nodes. Miliary tubercles were scattered through both lungs, the liver and the spleen. The marrow, studied both by smear and in sections, showed no pronounced abnormality.

This case, for which I am indebted to Dr. Rolfe Floyd, is an example of a much rarer condition than acute infectious mononucleosis. I have only found one other similar record, by Wiechmann in 1922, of a patient who died of miliary tuberculosis as shown by autopsy. Here, however, the mononuclears reached only 64 per cent.

There are many nonleukemic conditions where a distinct lymphocytosis is present, rarely however, so marked as to suggest a leukemia. In children, lymphocytosis is common in congenital syphilis, scurvy and rickets, and is characteristic of the blood picture in pertussis. In adults, lymphocytosis is associated with tuberculosis, malaria, hemophilia, typhoid, pellagra and other diseases. Increase in the number of lymphocytes has been reported in connection with the administration of thyroid extract, tuberculin, arsphenamin (Keidel and Moore in 1921) and pilocarpin. Minot and Smith (1921), reported abnormal types of leukocytes in tetrachlormethane poisoning. Cabot in 1913, pointed out the association of lymphocytosis in connection with streptococcic infections.

The blood of an acute leukemia may show a distinct preponderance of all small lymphocytes, such as makes up the blood of the great majority of chronic leukemias of lymphatic origin. On the other hand, the smear may show both a relative and absolute increase of the pathologically large mononuclear cells. It is this type of picture which causes such confusion and uncertainty in diagnosis. The socalled aleukemic leukemias, where the total leukocyte count is normal or subnormal, adds to the confusion, especially where there is no clue to the puzzle in a high proportionate number of lymphocytes. The prognosis of leukemia is uniformly bad and it is quite possible that such cases as have been reported by Ireland, Baetjer, Rührah and B. Gutmann and others, as acute leukemia terminating in recovery, belong in reality in the category of infectious mononucleosis. It must be remembered that there has been no case reported in which a patient suffering from acute infectious mononucleosis has developed an acute leukemia. The important question of a possible relation between these two conditions is at present no more than a matter for speculation.

**Summary.** In view of the cases presented, a high absolute and relative mononuclear count, persistent fever, and enlarged lymph nodes are not enough to establish the diagnosis of acute lymphatic

leukemia. This diagnosis must wait on the progressive development of symptoms and until repeated blood examinations have demonstrated thoroughly typical blood changes.

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## DIFFERENTIATION OF AMEBIC DYSENTERY FROM SO-CALLED IDIOPATHIC ULCERATIVE COLITIS.*

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and

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Amebic dysentery, while common in tropical and subtropical regions, is considered rare in patients seen by physicians in the Middle West portion of the United States, excepting those where there has been a definite infection contracted in the warmer climates. This opinion exists in spite of the fact that there are reports of amebic dysentery on record from more than half of the United States, including Illinois and many northern states. These instances of Entameba histolytica infection observed in Chicago emphasize the need for physicians, here and in other parts of the North, to be mindful of this type of dysentery in examining patients with chronic ulcerative colitis. Smithies' report of amebic dysentery in patients examined in Chicago mentions 27. Because of such reason by exclusion, amebic dysentery in this latitude is not considered seriously

* Read before the Chicago Society of Internal Medicine, January 26, 1925.

when patients with ulcerative colitis are examined. Haughwout recently has expressed a similar opinion.

During the past six months amebic dysentery has been demonstrated in 6 patients at St. Luke's Hospital, Chicago. These observations emphasize the need of careful examinations for amebæ in patients having symptoms of ulcerative colitis, and also emphasize again that amebic dysentery is not uncommon in these parts of the country. Of the 6 patients observed, 4 were treated successfully with emetin hydrochlorid. In the other 2 the disease was not recognized clinically and the diagnosis was made after death by postmortem examination. With 1 of these 2 patients the dysentery was considered to be of unknown origin because cultures failed to demonstrate in the stools bacteria of the dysentery types, and other examinations were not successful in disclosing the amebæ. The dysentery symptoms with the other patient were masked by other intraabdominal ones, and the ulcerative lesions of the large bowel were not known to be present until demonstrated by the postmortem examination. Motile amebæ, with red cell inclusions, were found in the exudate present in the abscesses of the mucosa.

As regards the source of the amebic infections, some can be traced quite definitely to a transient visit to southern states, but others seem to have been acquired in the North. How the latter infections occur offers considerable speculative thought. Infection anywhere probably comes by ingesting contaminated food or water. Vegetables or fruit grown in the South and furnished in season or out of season may be the means whereby people in these parts become infected. There is, of course, the possibility that the Entamœba histolytica is gradually being introduced into the northern climates and is adapting itself to the new environment. In this way the disease becomes endemic.

**Report of Cases.** CASE I.—C. M., a white man, aged thirty-four years, a salesman by occupation, was admitted to St. Luke's Hospital, February 14, 1924, because of diarrhea, flatulence, exhaustion, weakness and sleeplessness. The watery stools, which had commenced ten days previously and had often been as many as one per hour, were brown, contained blood, and their passage was accompanied by painful abdominal cramps.

Before the onset of the diarrhea, the patient had been well. Since then, he was unable to work but was not confined to his bed, and had been treated by his family physician, who gave him a milk diet and prescribed certain drugs without relief. The family and personal history of the patient are unimportant, excepting typhoid fever at the age of nine. As a traveling salesman, his territory included the northern parts of Illinois, Indiana and Ohio. He had never been in the South.

*Physical Examination.* The patient was moderately well-nourished, but seemed acutely ill. His temperature was normal.

There was a generalized tenderness of the abdomen but no palpable tumor masses. The liver dulness was normal, the spleen and kidneys not palpable. Rectal examination was not regarded advisable at this time because of the discomfort to the patient. All reflexes were normal. The blood examination demonstrated the following: erythrocytes, 4,930,000; leukocytes, 16,650; hemoglobin, 95 per cent. The Widal test (1 to 50) was negative. The urine had a specific gravity of 1.020, an acid reaction, and no albumin, sugar, erythrocytes, leukocytes or casts were found. Blood was present in the stools (chemical tests). Cultures of the urine and stools contained no typhoid or dysentery bacilli.

Ulcerative colitis of unknown origin was diagnosed.

*Treatment.* The patient was given a high-protein diet. Kaolin, charcoal and calcium chlorid in buttermilk were prescribed, and belladonna ($\frac{1}{6}$ gr.) was given three times daily. Codein, veronal and powdered opium were prescribed at various times when necessary for sleep.

*Course.* From the first to the fourteenth day the patient's condition remained practically the same, excepting for a temperature of 102° F. on the fourth day, and again on the tenth. Thereafter, the temperature varied between 100° and 102° F., reaching 103° F. on the sixteenth day. The stools continued to be frequent, bloody and liquid. The diagnosis of amebic dysentery was considered, but repeated examinations of warm stools failed to disclose any amebæ. It was not thought advisable to make a proctoscopic examination as the pain incident would be out of proportion to the information obtained.

Cultures of the feces on the third day contained only Bacillus coli; on the sixth day, again Bacillus coli; on the eighth and tenth days, Bacillus coli; on the sixteenth day, Bacillus proteus vulgaris appeared. Faint traces of albumin in the urine appeared as the disease progressed.

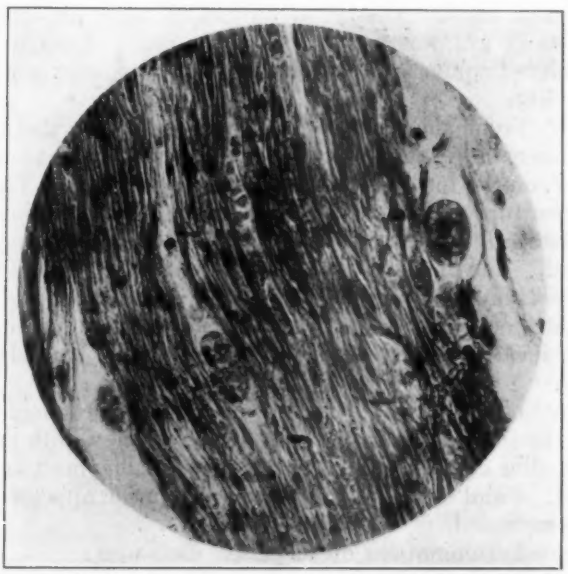
The blood examinations on successive days were:

| Day. | Erythrocytes. | Leukocytes. | Hemoglobin, per cent. |
|---|---|---|---|
| 1 | 4,930,000 | 16,650 | 95 |
| 5 | 3,980,000 | ..... | 70 |
| 8 | 3,925,000 | ..... | 79 |
| 13 | 3,880,000 | 13,950 | 70 |
| 15 | ..... | 26,250 | |

On the thirteenth day the patient complained of pain over the entire right side on palpation. Because of the symptoms of an acute peritonitis, an exploratory operation was decided on. Through a right rectus, muscle-splitting incision over the cecum, the abdomen was opened, and clear fluid was found in the peritoneal cavity. A stained slide preparation of this fluid contained many leukocytes, but no bacteria. Cultures prepared on blood agar and grown aërobically and anaërobically for forty-eight hours remained sterile.

While the surgeon was attempting to bring out the appendix for amputation, the extremely friable wall of the cecum was torn. No further surgery was attempted except to drain the cecum with a large rubber tube, and to close the abdomen loosely around the drainage tube. The patient's condition grew worse and death occurred three days after the operation.

*Necropsy.* By the usual postmortem examination of the trunk only, the essential changes demonstrated were present in the large bowel and rectum. The lining of the rectum was markedly reddened, especially below, and was covered with a thick yellow exudate. There was an ulcer 2 by 1.5 cm. just above the anus. It had an irregular red-brown base and was from 1 to 2 mm. in depth,



Microphotograph illustrating amebæ in the bowel wall near an abscess. × 560.

with its edges undermined. There were about fifteen dark red polypi as large as 3 cm. in their greatest dimension attached to the lining of the rectum at different places. There were also multiple hemorrhages in the rectal mucosa. There was a gradual fading of the reddened mucosa toward the sigmoid, and 15 cm. above the anal orifice it was gray-pink. The polypoid masses here also were dark gray and brown. The lining of the colon throughout its length was dark gray and was covered with a thick exudate. The mucosa as well as that of the rectum was irregularly roughened; its normal markings were lost and it had a moth-eaten appearance. The wall of the entire large bowel was friable and tore easily. Scattered irregularly over the lining were polypoid masses, ray-brown in

color and up to 3 cm. in their greatest dimension. There was a marked reddening of the cecum and the first 17 cm. of the ascending colon. The ileocecal valve was moderately reddened and edematous and on the front wall was an irregular hole, 3.5 cm. long, with necrotic gangrenous edges. The appendix was 9 cm. long and 1.4 cm. in diameter. The lumen was patent throughout, with the lining markedly hyperemic. The distal 5 cm. was a hemorrhagic necrotic mass. There was no ulceration of the lining of the small bowel nor were there abscesses of the liver. The cultures of the heart's blood grown on blood agar aërobically and anaërobically remained sterile; of the exudate on the bowel lining and of the peritoneal exudate these were identified: (1) Staphylococcus albus, (2) Streptococcus fecalis, and (3) Bacillus coli communior. Histological preparations of the bowel lining demonstrated an extensive suppurative inflammation of the mucosa. There were deep undermined ulcers extending down to and into the muscularis. Careful search in specially stained preparations demonstrated amebæ of the size described for Entamœba histolytica, and in their cytoplasm were engulfed red cells and other tissue fragments. In the granulation tissue spore forms were found.

CASE II.—E. H., a white man, aged forty-four years, entered St. Luke's Hospital, July 14, 1924, complaining of lassitude, a constant desire to defecate, watery stools with occasional mucus, pain over the lower abdomen and muscle soreness.

The onset occurred two months previously, while the patient was in Tennessee recuperating from an attack of pneumonia and a right empyema. Since that time the diarrhea had persisted, there being from five to fifteen watery stools a day, each accompanied by griping. The patient occasionally observed small amounts of bright red blood in the stools. He also had protruding painful hemorrhoids, and had been subject to attacks of muscle soreness and occasional joint pains. There had been no nausea, and no other complaints except a chilly feeling experienced early in the morning two weeks previous to admission. The patient felt well enough to be up and around.

*Physical Examination.* The patient was poorly nourished; he was not confined to his bed, but was weakened from the effects of the dysentery. Routine examination revealed nothing of importance except a tympanitic region over the transverse colon and the descending colon. The spleen and kidneys were not palpable. The blood count was: Erythrocytes, 4,650,000; leukocytes, 11,700, hemoglobin, 88 per cent.

A tentative diagnosis of amebic dysentery was made.

*Treatment and Course.* The patient was put on a fruit and vegetable-free diet. On the first day a rectal tube was inserted, and amebæ were isolated in the mucus recovered from the eye of

the tube. Emetin hydrochlorid (gr. 1 orally and gr. ½ hypodermically) was started at once.

The temperature remained normal throughout. The patient's condition improved; the bloody stools ceased, but they still remained soft, and frequent. The patient was discharged on the twelfth day with instructions to continue with the emetin hydrochlorid under direction.

CASE III.—G. R., a white man, aged sixty-three years, entered St. Luke's Hospital for observation, August 12, 1924, complaining of watery diarrhea, urgency and slight tenesmus, loss of weight, weakness and lassitude. The onset occurred six weeks previously, while the patient was in Louisiana. Since then the diarrhea had been continuous, there having been six bowel movements a day. On August 7, 8 and 9 he received three intramuscular injections of emetin hydrochlorid, but did not notice any change in his condition.

*Physical Examination.* The patient was well-developed, and apparently not in any pain or discomfort. Examination was negative, except for a slight tenderness on deep palpation over the descending colon. The blood count was: Erythrocytes, 4,165,000; leukocytes, 14,200, and hemoglobin, 90 per cent.

Microscopical examination of the mucus and blood in the stool demonstrated the presence of Entamœba histolytica in considerable numbers and actively motile. The urine contained a faint trace of albumin, occasional epithelial cells and many leukocytes.

Amœbic dysentery was diagnosed.

*Treatment and Course.* The patient received 1 gr. of emetin hydrochlorid intramuscularly, and was given instructions to continue this at home until 8 gr. had been taken in eight days. Then if the diarrhea subsided, treatment was to be suspended for a month and four more injections given. After another month's interval, this was to be repeated.

CASE IV.—G. S., a white man, aged eighty years, entered St. Luke's Hospital, July 24, 1924, complaining of diarrhea which began three weeks before while the patient was in Texas. There was a gradual increase in the frequency and watery consistency of the stools. At the most, they numbered six during a twenty-four-hour period. No blood was observed in the stools. There had been no griping, and the patient had been fairly comfortable. He had been treated by dietary methods (milk-toast diet). He did not know the source of the drinking water he obtained in Texas.

*Physical Examination.* The patient was fairly well-nourished. The ascending, transverse and descending colon were tympanitic. No abdominal masses were felt. The blood count was: Erythrocytes, 4,365,000, leukocytes, 8800, and hemoglobin, 89 per cent.

*Treatment and Course.* A proctoscope was inserted and mucous material was collected, in which motile amebæ containing ingested red cells were found. The patient was placed on a fruit and vegetable-free diet, and was given emetin hydrochlorid (gr. 1). Eleven days after admission no amebæ were found and the patient was discharged.

CASE V.—H. H., a white man, aged thirty-one years, complained of having cramps in the abdomen, diarrhea, bloody stools and loss of weight. This trouble had been persistent for two weeks, except when he took a morphin preparation which a physician had given him. The patient had about ten bowel movements a day; the stools contained bright red blood and mucus. He lost 14 pounds in weight and had become extremely nervous. He had lately been South as far as St. Louis.

*Treatment and Course.* Examination of the feces demonstrated amebæ. Emetin hydrochlorid was administered in a series of eight doses, starting with ¼ gr. and increasing to 1 gr. Four days later the bowel movements were quite regular and there was no tenesmus. During the following three days the patient had only one bowel movement a day. He was instructed to return after two months for another series of five injections.

CASE VI.—W. C., a white man, aged seventy-seven years, entered St. Luke's Hospital, September 24, 1924, complaining of diarrhea. The patient had been well and had carried on his work until about three weeks prior to admission. At this time he complained of some indigestion and constipation; he went on a diet and was apparently relieved for a few days. A week later he began to feel much worse with a pain in the left lower quadrant. He called an osteopath who gave him treatments. One week before entering the hospital he complained of severe pain and swelling of the big toe of the left foot—a gouty inflammation which he had had before. He was given colchicin for two days, which precipitated a diarrhea. For two days before entering the hospital he had blood in the stools.

Six years before the patient's present illness, he had an attack of dysentery the cause of which was not determined.

*Physical Examination.* The abdomen was somewhat distended and there was a definite resistant mass in the left lower quadrant. There was a non-movable dulness on percussion in the left flank. There was a leukocytosis of 18,000 and a temperature of 100° to 102° F. On account of these symptoms a diagnosis was made of a localized peritonitis due to some inflammatory condition in the region of the sigmoid flexure and it was thought that an ulcerative condition of the bowel was responsible for the blood. The stool contained mucus and blood, but no dysentery bacilli. The advisability of a laparotomy was discussed with a surgeon but was not deemed advisable.

For three days the patient gradually grew weaker, tympanites increased, and death occurred on the fourth day.

*Necropsy.* The essential changes demonstrated by the postmortem examination of the trunk only were limited to the large bowel and rectum, excepting a slight generalized acute serofibrinous peritonitis. In the lining of the colon and rectum there were multiple, closely-set abscesses up to 2 cm. in their greatest surface dimension. They contained a thick yellow exudate. In the rectum there were undermined ulcers of about the same size. There was a marked edema of the mucosa lining the large bowel and the rectum. Examination of the exudate on a warm stage demonstrated large numbers of Entamœbæ dysenteriæ.

**Discussion.** The confusion and bewilderment attendant on the diagnosis of acute ulcerative colitis has been due, in part, to the great variety of entities that have been included under the title of this disease. Practically speaking, the present discussion is limited to those cases of acute ulcerative colitis characterized by a sudden onset and speedy termination in death, without the cause having been determined soon enough to treat successfully. One writer speaks of it as being "a disease of the postmortem table." Hitherto it has been unfortunate that in many of these cases we have not been able to diagnose the disturbance during the lifetime of the patients, and hence our studies have been confined to the postmortem aspects of the disease; consequently, only the more severe features could be studied.

There are many different acute forms of ulcerative colitis: it often appears in infants, or accompanies chronic (infective) endocarditis and chronic dysentery, and occurs in terminal conditions in certain chronic diseases, especially nephritis. Lastly, there is the innominate form of ulcerative colitis, and it is this form with which this paper deals.

In order to avoid misunderstanding as to the type of colitis under consideration, we may list the recognized criteria of true acute ulcerative colitis of unknown origin as follows: (1) Diarrhea, more or less persistent, with stools frequent in number and possessing dysenteric characteristics; (2) the presence of blood in the stools at some time or another, with or without mucus, sloughs and pus; (3) abdominal pain, general or local, with or without rectal pain; (4) some degree of fever; (5) loss of flesh, and (6) duration of the disease for longer than one week.

Acute ulcerative colitis, apart from the form known as tropical dysentery, has been considered so fatal a disease that some writers think that there is no cure for it, and that cases diagnosed as such, which have resulted in recovery, could not have been true forms of acute ulcerative colitis. Our experience would appear to disprove this. Acute ulcerative colitis of unknown origin is so rare and so fatal that men have tacked on the terms "idiopathic" and "innomi-

nate" to its name, the literature has been so cluttered up with the many different types of dysenteries, and experimental evidence has been so diffuse that we wonder whether there is such a thing as "acute ulcerative colitis of unknown origin." Of course, we are aware of the confusion that exists between acute ulcerative colitis and tropical dysentery—a confusion which is still far from being ended—and certainly we would not go so far as to say that all cases of acute ulcerative colitis are examples of tropical dysentery—still, when we find two cases that fit, in every detail, into the clinical picture of acute ulcerative colitis, and which are found to be amebic in origin, we question whether many of the cases reported in the literature as being acute ulcerative colitis of unknown origin would not have been found to be cases of amebic dysentery if proper time and study to the microscopical examination had been given by competent laboratory workers.

There may be some difficulty in demonstrating the organisms in the chronic state especially when considerable portions of the bowel lining have been destroyed. Repeated examinations should be made with these. The amount of mucosa regenerating after an extensive suppurative inflammation may not permit complete healing and in these patients, even after emetin treatment, a chronic suppurative inflammation will persist.

We have reported these other cases of amebic dysentery to show that this disease is not so rare as it has been considered in the literature bearing upon this type of colitis. Another reason, perhaps, why cases of amebic dysentery have not been reported is that there is nothing unusual about them, and the etiology and histology have been so well worked out that the majority of men thought them not unusual enough to report.

In combating desperate cases where the diarrhea is distressing, the practitioner is armed with a long list of drugs, such as the following: Tannigen, bismuth subnitrate, bismuth salicylate, flushings of 1 per cent tannin or 1 to 1000 salicylic acid; aromatic sulphuric acid, antiseptic betanaphthol and phenol salicylate, thin starch to which from 20 to 30 drops of laudanum has been added; nitrate of silver and sulphate of copper; acetate of lead, and alterative doses of castor oil, ½ dram after meals. He uses these singly or in combination, finally coming to the conclusion that he is powerless to control the diarrhea, because he has been unable to find the right drug or the right combination of drugs. The literature is full of case reports listing the usual variety of remedies used to check the diarrhea, and which inevitably end with the worn-out statement that they have "failed to check it."

In trying our various drugs which have been handed down for years and years (and each few years adds a new one to the list), we have discovered that unfortunately this type of dysentery is not influenced by any of them. From our experience, though, it would

seem that the empirical use of emetin might be effective in some of the cases which have baffled the diagnostician. Incidentally, at this point we should like to warn particularly against an opinion that is very prevalent, namely, that when moderate doses of kaolin fail to combat this diarrhea, massive doses of 4 or 5 ounces a day should be given. It is obvious that large doses of barium or kaolin may cause a perforation of the intestine.

We have all felt that since the advent of the proctoscope and the roentgen-ray, the diagnosis of the dysenteries would be rendered relatively simple. It is unfortunate, however, that we cannot look to either of these instruments of precision as an aid in diagnosing these cases. In the majority of cases we are forced to exclude the use of both the roentgen-ray and the proctoscope, because of the danger of rupturing the intestine. It is the rapidity with which the colon becomes necrotic that makes both the barium meal and the proctoscope such dangerous procedures to use, as borne out by the fact that in one case an operation was performed twenty-three days after the appearance of the first symptoms, and the colon could not be picked up without its being ruptured. In the case of desperately sick patients we are often not justified in submitting them to the routine of the roentgen ray or proctoscopic examination. For instance, there was no period in the course of the disease in Case I which we could have chosen as the proper time for such an examination, and it presumably was just as well, for we would undoubtedly have caused a perforation at almost any time after the patient came under our observation.

With possession of these facts, how amazed one is to read a recent article in a report of 250 cases, in which the author makes this statement: "The failure to detect early the large number of diseased conditions in the terminal colon results from a neglect to examine all patients with the sigmoidoscope, however slight the symptoms." This is a typical modern statement, and gives voice to an unfortunate modern conception of making diagnoses. There is no possible way to detect from the condition of the patient the condition of the colon, and therefore we should be alert to the accidents that could happen with such instruments as the proctoscope—accidents which often are never discovered unless a necropsy is performed. It is rather surprising to find that, with the great number of cases reported in this article, there seems to be no contraindication to this drastic procedure. We could leave it to the imagination to picture what would happen to a colon following the insertion of a proctoscope or the passing of a rubber tube to the sigmoid; or irrigation (silver nitrate, argyrol), when, as in Case I, in two weeks from the onset of the disease the colon was found at operation to have the consistency of wet blotting paper.

Operations in this type of case are usually delayed and performed only as a last resort. We are so unaccustomed to thinking that the

"last resort" of a dysentery occurs within such a short time as it did in Case I that it would be impossible to think that an ileostomy could have helped the patient unless it had been performed two weeks after the onset. The lack of experience of surgeons and the lack of early guiding symptoms cause us to neglect operating in these cases early enough to be beneficial.

Thanks are due to Dr. Joseph M. Miller for the privilege of reporting 2 cases of amebic dysentery, to Dr. Joseph Capps for the privilege of reporting 1 case, and to Dr. Eugene Talbot for another case.

**Summary.** 1. The possibility of amebic infection in patients with a chronic ulcerative colitis should be considered, and there should be a search for amebæ before a diagnosis of idiopathic ulcerative colitis is made.

2. The usual medication including large doses of kaolin, bismuth, and other astringents is not indicated where the infection is definitely amebic.

3. Because of the extensive ulceration and friability of the bowel wall with amebic dysentery, the proctoscope should be used with extreme caution.

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## DUODENAL DIVERTICULOSIS, WITH REPORT OF A CASE SEEN ROENTGENOLOGICALLY.

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Up to the year 1912 duodenal diverticulosis was actually unknown clinically. In reviewing the literature on the subject Case[1] found that 82 cases of duodenal diverticula had been reported from 1761 to 1911.

In 1915 Case[1] himself reported a series of 7 cases he found in routine roentgenologic examination of the gastrointestinal tract; later, in 1920,[2] he again reported on a sum total of 85 cases of diverticula of the small intestine in 6847 complete barium-meal studies.

Other authors, such as Akerlund,[3] Cullen,[4] Cole and Roberts,[5] Holzweissig[6] and many more have since contributed to our knowledge of this entity and impressed the profession with its greater frequence as well as the dangers that may at times accompany this condition. Constant perfection in technic is no doubt responsible for the ever increasing number of cases detected during roentgen-ray examination of the gastrointestinal tract.

Although this subject has been so fully and thoroughly considered by various authors, yet it would not seem amiss to add the following case to the list of those already reported, for these reasons: (*a*) Relative infrequency of duodenal diverticulosis; (*b*) multiple diverticula in the case illustrated; (*c*) infrequence of the location of one diverticulum ($D^2$); (*d*) size of the diverticular shadows.

It is interesting to note that this patient gave no symptoms that were directly attributable to the diverticulosis.

**Case Report.** Mrs. M. N., aged sixty-five years, housewife, complained of diarrhea of four months' duration, manifesting itself in five to six bowel movements a day, this being associated with abdominal distention and at times cramps about two hours after the ingestion of food. Her family history as well as the past history is essentially negative. The present complaint dates back to four months ago when she was taken ill with what she called a "nervous breakdown." This condition lasted for a period of four weeks. At present in spite of her general condition being much improved the gastrointestinal symptoms are still persisting. There is no loss of weight, appetite is good and there is no abdominal pain.

Physical examination reveals nothing of importance, with the exception of considerable abdominal distention and diffuse tenderness throughout the abdomen.

Laboratory findings: The urine examination is negative. Examination of gastric contents showed the total amount aspirated one hour after an Ewald meal to be 35 cc, with a total acidity of 20 degrees; free hydrochloric acid, 10 degrees; no occult blood; microscopical examination is negative. Stool examination is negative.

Roentgenographic examination of the gastrointestinal tract reveals a marked gastrointestinal hypermotility which is not referable to any visible organic lesion; also the duodenal diverticula as shown in the accompanying illustrations are visualized.

Attributing this hypermotility to a gastric hypochlorhydria and treating her on the basis of this presumption, I succeeded in checking the diarrhea quite promptly.

At present the patient's condition is good. The diverticula found have obviously no bearing on the above described symptomatology, and she refuses to consent to an operation.

**Discussion.** As to the etiology of this anomaly, a number of opinions have been offered by various authors. Some of these cases are no doubt congenital in origin, since they have been found in

infants. Nevertheless, age seems to play an important role as an etiological factor, a great majority of cases being found in the

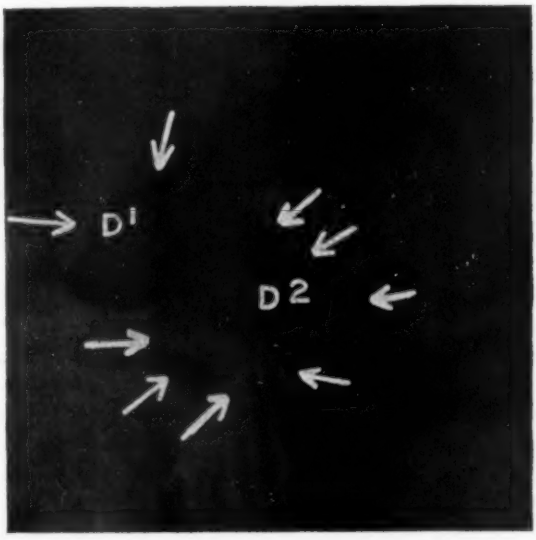


FIG. 1.—Roentgenogram showing duodenal diverticula. $D^1$ is a diverticulum in the second portion and $D^2$ a diverticulum in the transverse portion of the duodenum.

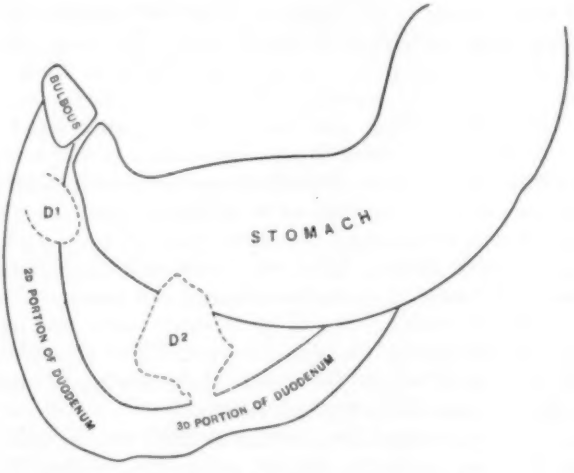


FIG. 2.—A diagrammatic representation of Fig. 1; $D^1$ and $D^2$ representing the diverticula.

seventh and eighth decades of life. This can perhaps be attributed to a loss of elasticity in certain parts of the intestinal wall, which

may accompany old age; or may be associated with an increased intraintestinal pressure. Such a condition may be the result of a chronic ileal or colonic stasis or perhaps repeated localized intestinal spasms.

Holzweissig[6] in 1921 contributed a very thorough and lengthy discussion concerning the etiology of duodenal diverticulosis, wherein he attempted to prove with the aid of stained preparations of sections of the intestinal tract, that the piercing of the intestinal musculature by the bloodvessels create loci minoris resistentiæ, permitting the mucosa of the intestine to form herniæ through the musculature.

The piercing of the second portion of the duodenum by the common bile duct and Wirsung's duct may operate in the same manner in the production of a diverticulum. These diverticula are spoken of by the French authors as the "peri-Vateran" diverticula, and these cases constitute a high percentage of this anomaly.

Other factors which may enter into the etiology of these diverticula are chronic peptic ulcers, chronic cholecystitis with cholecystoduodenal adhesions, cholelithiasis and recurrent attacks of duodenitis.

These diverticula are usually single; sometimes, however, as many as three and four may be found, and these are at times associated with a colonic diverticulosis. They vary in size from a pea to that of a small pear. In Case's series the average size of the shadow of the barium filled diverticulum was 2.8 cm. In the case reported here the greatest diameter of the diverticular shadow, as seen on the original film measures 6 cm. The most usual sites for these duodenal pouches, as they are found in their order of frequence, are: In the second portion of the duodenum 57.5 per cent; in the third portion and the duodenojejunal junction, 22.5 per cent; in the first portion of the duodenum, 20 per cent.

Upon examination these diverticula present an arrangement of structures comparable to that of a true aneurysm in which the intima has herniated through the outer coats of the vessel. They are composed of a mucosa lined with a smooth epithelium, which may show, as a result of distention thinned out areas. The glands of Lieberkühn as well as bits of pancreatic tissue are frequently found in the mucosa of the diverticulum. The muscularis coat, as a rule, is absent except for a few fibers scattered around the opening leading into the intestinal lumen.

About the symptomatology nothing definite can be said, as this condition does not present a definite symptom complex whereby a positive diagnosis may be established. Most of these cases are detected during the course of routine roentgen-ray examination of the alimentary tract. In some of these, however, the diverticulum may cause retention of large quantities of food, resulting in periodic intestinal attacks of a toxic nature, with or without pain. At

times these attacks may simulate those of a chronic or even acute ileus. Perforation of the sac with a fatal outcome has also been reported in the literature.

**Summary.** A case of duodenal diverticulosis, showing two diverticula in the second and third portions of the duodenum respectively, with roentgenographic findings, is reported.

The infrequence of this condition is pointed out, Case reporting characteristic evidence of duodenal diverticulosis in about 1.2 per cent of 6847 cases radiographed.

The most usual sites of these diverticula in their order of frequence are mentioned, namely: In the second portion of the duodenum, 57.5 per cent; in the third portion and duodenojejunal junction, 22.5 per cent, and in the first portion of the duodenum 20 per cent.

Various theories as to the etiology of this anomaly are quoted; the actual factors operative in its production are no doubt obscure in many cases.

The great majority of cases do not at any time present any definite symptomatology; they are usually discovered in the course of a routine roentgen-ray examination of the alimentary tract.

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## THREE CASES OF TULAREMIA, ONE RESEMBLING SPOROTRICHOSIS.

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The occurrence of proven cases of tularemia in man has been reported from so many different parts of the country that its widespread nature is manifest. Details of its history and etiology are here omitted, as they are described elsewhere.

The three following cases were found in game dressers in the Huntington market:

**Case Reports.** Case I.—C. W., a married white man, aged thirty-one years, was referred to the writer by Dr. I. W. Mayberry, because of the continued recurrence of abscesses on the left arm

and forearm. His present illness began on November 20, 1924, with a dusky red spot on the proximal phalanx of the middle finger of the left hand. Previous to this time he had been so well that he had never consulted a physician.

*History.* The beginning of the open season for rabbits was on November 15, on which date he first dressed one, and it was five days later that the sore appeared. The finger became enlarged and tender, as did the two adjacent ones; the temperature went

Case I.—This shows the initial finger lesion, the draining axillary incision and the purplish-red scars. Over the biceps there is an early, deep-seated, indurated nodule.

to 103°, at which it continued for seven days, accompanied by delirium. The primary sore broke, and much pus was evacuated. He was confined to his bed for eighteen days, and was treated for "flu pneumonia." At the end of this period he noticed the appearance of an enlarged tender gland in the axilla of the affected limb, and also the formation of a scum over both eyes, followed by small yellow bumps on the conjunctivæ. The axillary gland was lanced, a large amount of pus being obtained. The conjunctivitis dis-

appeared in time, but small lumps continued to appear at intervals on the left arm and forearm, only one appearing elsewhere, this being over the twelfth thoracic spine. The distribution was quite irregular. They appeared first as deep, tender, indurated nodules, the overlying skin being freely movable and not discolored. The nodules gradually enlarged to a diameter of 0.5 to 2 cm., and in five to seven days fluctuation developed, with sometimes a purplish discoloration of the overlying skin. Upon deep incision, a thick, light green material was obtained. The pain was thereby relieved, and the wound always healed well, never to give any further trouble. He continued to run a slight fever at intervals until March 20, after which the temperature has remained normal.

*Physical Examination.* March 20 (condensed). The patient is thin, of fair muscular development and anemic. His weight is 150 pounds, the normal being 170; he is gaining at present. The skin has a normal texture and moisture over the body. Over the left arm and forearm the purplish red scars of many abscesses are seen and one deep, indurated nodule over the center of the biceps. The first abscess, which appeared in the axilla, continues to drain slightly at intervals. The skin over the left hand has a peculiar purplish-red color, and the extremity is colder than the other one. The cervical, axillary, epitrochlear and inguinal nodes are not enlarged. The tonsils, teeth and sinuses show no abnormalities. The heart, lungs and the abdominal viscera are normal. The temperature is 99.3°; the pulse, 100; the blood pressure: systolic, 118; diastolic, 70.

*Laboratory Examinations.* The urine shows a distinct trace of albumin; no sugar. There are four small hyalin casts per low-power field. Blood: White blood cells, 12,900; polymorphonuclears, 68 per cent; lymphocytes, 27 per cent; mononuclears, 3 per cent; eosinophils, 2 per cent; red blood cells, 4,208,000; hemoglobin, 68 per cent Sahli; color index 0.8, red cells are normal in shape and staining properties. Serological: The Wassermann test is negative; the agglutination test with bacterium tularense, done at the Hygienic Laboratory in Washington by Dr. Edward Francis, was positive in all dilutions from 1 to 10 to 1 to 640 and negative in higher dilutions. Bacteriological: Microscopical examination of the green discharge from the lesions showed necrotic material containing no microörganisms. Repeated cultures on glucose agar, glucose broth and Sabouraud's maltose agar were negative. A guinea pig inoculated with the material remained well.

*Roentgen-ray Examination.* Roentgen-ray examination of the bones of the left arm and forearm was made because of the similarity to sporotrichosis, which exists in this region. No bony cysts were found, nor was there bone involvement of any kind.

*Treatment.* This was symptomatic until February 20, when first seen by the writer, when a diagnosis of sporotrichosis was made.

The patient was given the iodides, after which only one more nodule developed, and the temperature became permanently normal in ten days.

CASE II.—M. B., a white married man, aged twenty-six years, was a friend and co-worker of the first patient. Prior to the present illness he had been very healthy.

During November, 1923, the open season for rabbits he cut his left hand between the thumb and index finger while dressing one. The wound became very sore, and the infection traveled to the axilla. The temperature went to 103.5°, and he was confined to his bed for three weeks, being treated for pneumonia. The axillary glands became larger and more painful, and were lanced, a large amount of pus being obtained. He was kept from his work for four months, and even after that time was weak, improvement taking place very gradually. These two lesions were the only skin manifestations. He had no conjunctivitis. His normal weight was 145 pounds, but during his illness he fell to 120 pounds. At present he has regained his lost weight. The patient was not seen until after his complete recovery, hence the omission of details.

The blood serum was sent to Dr. Francis for an agglutination test with Bacterium tularense. He reported a positive in all dilutions from 1 to 10 to 1 to 40, but negative in higher dilutions. Dr. Francis states that he has never found a human serum other than tularemia to agglutinate in this dilution.

CASE III.—G. K., a bachelor, aged sixty-two years, was employed in the same capacity, and in the same place, as the two patients above reported. On December 18, 1923, he was taken ill with fever, and a sore on his right hand between the middle and the ring fingers. An abscess formed, which broke on Christmas morning, discharging a green pus. It continued to drain for six weeks, and he was kept from work until April. Even at that time he felt weak, and was but slowly regaining his lost weight. He recalls no axillary soreness. At present there is no cervical or axillary enlargement. His affected hand is partly drawn and cold. Some disability still exists, due to the pull of scar tissue. There was no skin manifestation other than the abscess mentioned, and no conjunctivitis.

Serological findings: On April 15, 1925, an agglutination test for tularemia was done by Dr. Francis, who reported it positive in dilutions of 1 to 20 and 1 to 40, but not in higher dilutions. He states that that is the titer of his own serum five and a half years after his attack. The blood Wassermann test on this same date was negative.

**Comment.** In the first case the close resemblance to sporotrichosis is of special interest. The method of onset, the positive

agglutination tests with Bacterium tularense, the persistently negative cultures, the negative guinea-pig inoculation and the absence of bone cysts serve to prove that it was not a yeast infection. The occurrence of a conjunctivitis, probably tularemic, is also noted. The improvement after iodid administration probably was coincident with the improvement naturally taking place.

The other cases correspond closely to ones described elsewhere, and are reported because of the comparative newness of the disease.

**Conclusions.** Three cases proven to be tularemia are reported, all of which were contracted from handling infected rabbits. One case resembled sporotrichosis, and had a complicating tularemic conjunctivitis. The others ran a course similar to the average described case. No treatment of proven merit was employed.

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## MALIGNANT TUMORS OF THE THYROID: AN ANALYSIS OF SEVEN CASES WITH A STUDY OF THE STRUCTURE AND FUNCTION OF THE METASTASES.

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NEW YORK.

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Malignant disease of the thyroid is of especial interest to the clinical pathologist, because the peculiar function of the tissue in which it grows affords a criterion for the study of the physiology of the malignant tissue cell, which is not possible in malignancy elsewhere in the body. The disease is comparatively rare. L. B. Wilson[1] has collected from the records of the Mayo Clinic and from the literature 972 cases of which number about 80 per cent are of the carcinomatous type. In the incidence of malignant tumors in general, the disease plays only a small part. Among 40 cases of sarcoma and 624 cases of carcinoma admitted to Montefiore Hospital from July 1, 1914 to July 1, 1924, there were only 8 cases (1.2 per cent) of malignancy of the thyroid—1 sarcoma and 7 carcinomata. Of these, 1 case has been reported by Skversky[2] and will not be included in this series.

It is the opinion of most writers that malignant disease of the thyroid seldom, if ever, occurs primarily in a healthy gland. It is believed to be preceded always by pathological changes, most commonly of the adenomatous type, which Balfour[3] looks upon as the premalignant condition of the thyroid. Speese and Brown found that benign tumors preceded the development of malignancy in practically every one of their cases of cancer of the thyroid. This

has not been our experience. Only one of our cases gave a history of a swelling in the thyroid region previous to the onset of clinical symptoms of malignancy.

The incidence of malignant disease of the thyroid is greatest in those regions where goiter is most frequent. Limacher[4] in Berne, where goiter is very common, in 7461 routine autopsies, found 82 cases (1.09 per cent) of malignant disease of the thyroid, while Huguenin[5] in Guenf, where the incidence of goiter is not so great, in an almost similar number of autopsies (7356), found only 25 cases (0.35 per cent) with malignancy of the thyroid. Its greater incidence in people with a definite evidence of goiter, (1.9 per cent in a series of 14,456 cases in the Mayo Clinic), as compared to its occurrence among the general population that come to routine autopsy (0.0027 per cent), points in the same direction.

The age incidence of malignant disease of the thyroid is about the same as that of malignancy elsewhere in the body, except that sarcoma does not here show its characteristic predilection for the earlier age groups. The greatest incidence is in the fourth and fifth decades (6 of our 7 cases), but about 20 per cent of all cases occur under forty years.

The disease is more common among females, (7 to 3 in the Mayo Clinic cases; 5 to 3 in our series) in whom goiterous enlargements of all kind are also more frequent.

**Pathology.** Sarcomata and carcinomata are found. The latter were divided by Langhans into seven types. The most common, probably, is the simple carcinoma composed of solid strands or masses of atypical cells showing no alveolar differentiation. Metastases showing well marked alveolar formation were at one time looked upon as disseminated nodules of benign thyroid tissue from a "metastasizing colloid goiter" or from a proliferating adenoma. It has since been definitely shown that these are true carcinomatous metastases, occasionally found together with the solid type and due often to a small, even microscopic primary carcinoma of the thyroid. Papillary carcinomata, either solid or cystic in type, are occasionally found. Squamous-cell carcinomata are rare. They are derived from the remnants of the thyroglossal duct. The "postbranchial goiters" are so named from their reputed derivation from the postbranchial body. Parastruma is the name applied to masses of large, clear cells resembling somewhat those of the normal parathyroid.

The sarcomata are of various cellular types. Round cell, spindle cell, mixed cell and occasionally giant cell varieties have been described. We have seen a lymphosarcoma of the thyroid, but there was nothing to indicate that this was its primary seat of origin. The structure of these varies from that of a typical fibrosarcoma to an alveolar arrangement strongly resembling the alveolar types of carcinoma. The histological as well as the clinical

differentiation between sarcoma and carcinoma is not as well marked in the thyroid as it is in other organs. Cases have been described showing both a sarcomatous and a carcinomatous structure in the same tumor. So poorly marked is the line of differentiation between these two types of malignancy that Ewing[6] is unwilling to believe that the so-called sarcomata of the thyroid are of true mesoblastic origin. He regards them rather as essentially ectoblastic tumors with a hyperplastic stroma.

**Symptoms and Clinical Course.** The disease usually begins with the appearance of a swelling at the base of the neck or with the sudden onset of growth in a long-standing goiter. The local condition may be of various degrees of prominence leading to the formation of a tumor of various size up to that of child's head and forming the initial and out-standing symptom of the disease by the resulting compressive phenomena. Occasionally, however, the local symptoms are a negligible factor; there may be absolutely no visible or palpable lesion in the thyroid and the whole picture may be dominated by the metastatic phenomena. In a case from this hospital reported by Skversky,[2] the patient, who complained of pains in the legs, had been treated for neurasthenia and for osteitis of the lumbosacral region. Autopsy showed metastases to the spine from a very small carcinoma of the thyroid, which, during life, had attracted no suspicion whatever.

Metastases may or may not take place. When present they may occur at any time during the course of the disease and the dissemination may be by the lymphatics, by the blood stream or by both. The most frequent site of lodgment is the lungs, next the osseous tissue, then less commonly the liver, kidneys and pleura. Cancer of the thyroid stands out prominently among carcinomata elsewhere in the body as being the most prone, next to cancer of the breast and possibly of the prostate, to metastasize to the skeleton. The skull, inferior maxilla, sternum, the long bones and the pelvis are invaded in the order of frequency mentioned. The skeletal metastases are of the osteoclastic type, there being usually no sign of any attempt at new bone formation. Occasionally, however, especially in the sarcomata, osteoplasia does take place. We have seen at least one case where bony union has taken place after a pathological fracture induced by a metastasis of a sarcoma of the thyroid.

The disease usually runs its course in from two to four years. Acute fulminating types have been described with inflammatory symptoms causing death in a few weeks from general dissemination. Cases of the adenomatous type are inclined to have a more prolonged course. Sarcomata are said to be rapidly fatal, yet one of our cases (Case V) with a metastasis to a rib is alive and engaged at fairly arduous work three and a half years after the clinical onset of the disease.

**Case Reports.** The following cases were treated at Montefiore Hospital during the six years from 1918 to 1924. The reports of 3 of these are taken from the records; the remaining 4 were seen personally.

CASE I.—B. K. (1782), a man aged forty years, was admitted on June 9, 1918, with a history of severe, cutting, cramp-like pains in the left groin radiating into the left testicle and upward into the left lumbar region, commencing in July, 1917. This was followed by severe pain in the entire back and in the right hip and by the appearance of many small swellings over the ribs and behind the ears. There was a loss of 50 pounds in weight. Physical examination disclosed a very hard, non-tender tumor the size of a pigeon's egg adherent to the deep fascia of the front of the neck and to the laryngeal cartilage. Scattered all over the chest were many very painful, tender, oval masses ½ to 1 inch in diameter, firmly attached to the underlying tissue but not to the skin. Roentgen-ray examination showed irregular bone destruction all over the left side of the pelvis and left femur, in the bodies of the vertebræ and in the ribs, with multiple pathological fractures in the latter. Clinical course was marked by the appearance of new masses over the ribs until the patient's death on September 9, 1918. No autopsy was obtained but the clinical diagnosis seemed definite.

CASE II.—D. K. (4233), a man, aged fifty-one years, was admitted on May 11, 1921, giving a history of having had a hard tumor on the right side of the neck gradually enlarging until four years ago when it had reached the size of a small orange, causing difficulty in breathing and swallowing. Operation at Mount Sinai Hospital on September 15, 1920, revealed a tumor of the thyroid which, on examination by Dr. Geist, proved to be a "medullary carcinoma." One month after operation patient began to have pain in the upper chest and in the left elbow with loss of function in the latter. There was great weakness and loss of 35 pounds in weight. Examination showed the entire region of the thyroid, both sterno-clavicular articulations and the manubrium sterni to be dominated by a massive, hard, nodular tumor attached at its base. There was marked increase in submanubrial dulness. There was a tense swelling of the left forearm with ankylosis of the elbow. Roentgen-ray showed an intrathoracic mass continuous with the thyroid tumor and extensive destruction of the lower end of the humerus. Patient left the hospital of his own accord on June 25, 1921.

CASE III.—L. Y. (9616), male, aged forty-eight years, was admitted on May 9, 1922, with a history of the appearance of two small nodules on the left side of the neck eighteen months previously. These had rapidly increased in size and were removed at Beth

David Hospital. Shortly after the operation the patient developed shooting pains in both legs. Examination showed the sternal end of the right clavicle to be thickened, forming a bony tumor the size of a hen's egg. There was a soft movable mass over the left apex. Roentgen-rays showed destruction throughout the right clavicle, humerus, ilium and femur. Course was gradually downward until patient's death on February 17, 1923. No autopsy was obtained.

CASE IV.—J. B. (11,153), female, aged seventy-two years, was admitted May 7, 1923. First symptom was the onset of snoring during sleep three years before admission, followed by slight dyspnea and the appearance of a small indurated swelling in the thyroid region. Tracheotomy was done at the Memorial Hospital to relieve dyspnea and at the same time a biopsy was done which showed a papillary adenocarcinoma of the thyroid. Examination showed a moderately cachectic woman with a hard mass about 3 cm. by 3 cm. in size in the thyroid region. Roentgen-ray studies revealed no metastases. Clinical course was marked by progressive increase in the size of the mass, in the dysphagia and the cachexia until the patient's death on March 6, 1924.

CASE V.—G. B., female, aged fifty-five years, first seen at the Radium Clinic on May 2, 1923, gave a history of having noticed the appearance of a nodule the size of a pea on the right side of the neck in February, 1922. This had gradually increased in size. She had been given two radium applications at one month's intervals followed by operation at Mount Sinai Hospital by Dr. A. V. Moschkowitz, at which an encapsulated mass involving the right lobe and isthmus was removed and found on microscopical examination to be a papillary adenocarcinoma of the thyroid. Her only complaint when first seen was a slight difficulty in swallowing. Examination showed a diffusely indurated area in the tissue between the skin and the larynx and a slight increase in retromanubrial dulness, otherwise entirely negative. Roentgen-ray examination showed a substernal thyroid. No clinical or roentgenological evidence of local recurrence or of metastases could be found on repeated examination. Patient has been given surface applications of radium over the thyroid region and prophylactic roentgen-ray treatments over the chest and pelvis and is now apparently well, with no sign of any recurrence two years after the operation and three years after the clinical onset of the disease.

CASE VI.—H. S., male, aged forty-four years, was first seen at the Radium Clinic on July 1, 1923. About two years previously patient had noticed in the thyroid region a small swelling the size of a pebble which had since increased in size. About eight months previous to date first seen, patient after slight exertion had felt

what he thought was a rib cracking on the right side of the chest and had considerable pain on breathing thereafter. Biopsy specimen from the rib done at Mount Sinai Hospital was examined by Dr. Mandelbaum and found to be a mixed-cell sarcoma with round and spindle cell elements. Examination on admission showed an asymmetrical enlargement of the anterior surface of the neck forming a mass 7 cm. by 9 cm. by 3 cm. which moved on deglutition, was not tender and did not interfere with breathing or swallowing. Roentgen-ray examination showed a large mass, evidently the thyroid, pushing the trachea to the right and partially compressing it. There was a fusiform mass over the middle third of the eighth rib on the right side with considerable bone absorption in this region. Repeated pictures of this mass showed a slight but definite decrease in size and increase in density. Patient is now apparently well and engaged at fairly arduous manual labor three and a half years after the clinical onset of the disease. Treatment given is the same as in the previous case.

CASE VII.—This case is reported in more detail because of its unusual clinical interest and because it was made the basis of a study which may perhaps throw some light on the pathology of this type of cancer.

P. S. (11,855), female, aged fifty-two years, was admitted on June 21, 1924. Her illness began in the summer of 1922 with the sensation of a lump in the throat accompanied by a difficulty in swallowing. In October, 1923, the patient began to have burning pains in the left side of the chest radiating down the left arm and several weeks later noticed a small, hard, painless lump in the right breast just above the nipple. About December, the patient began to have aching pains down the back of both legs and about the same time it was noticed that her voice was becoming husky. By March, 1924, the mass in the right breast has grown considerably, a definite swelling had become noticeable at the left side of the base of the neck, a small nodule had appeared over the right hip and another over the right frontal region. In April, the patient's left eye was noticed to be becoming increasingly prominent, while just before admission a nodule appeared in the left occipital region at a point where the patient had struck her head against the bed-post about three weeks previously.

Physical examination showed a moderately emaciated, middle-aged, bed-ridden woman. The scalp showed a hemispherical, fluctuating swelling about 4 cm. in diameter fixed to the underlying tissue in the right frontal region; a similar smaller nodule in the left occipital region. There was protrusion of the left eye with limitation of motion in all directions and complete loss of vision. The right eye was normal except for a slight congestion of the fundus; the left showed a definite primary optic atrophy. There was lagging

of the left faucial arch and laryngoscopic examination showed fixation of the left vocal cord.

There was a hard, nodular, irregular swelling in the middle of the left side of the base of the neck, displacing the trachea to the right. The mass was about 7 cm. by 4 cm. in size, moved with deglutition, and the veins overlying it were turgescent. There was no cervical adenopathy.

In the vault of the left axilla was a hard, smooth mass about the size of a hen's egg, fixed to the surrounding structures. Just above the level of the scapular spine in the left paravertebral region was an immovable, non-tender, fleshy mass about the size of a walnut. There was some tenderness on pressure along the dorsal spine. Percussion showed an increase in the retromanubrial dulness on the left side. Auscultation showed harsh breathing at the bases and an occasional moist rale at the apices. The heart and blood vessels were essentially negative.

The abdomen showed turgescence of the superficial veins. There was a small, hard, freely movable nodule over the right hip near the posterior superior spine. The liver was not enlarged but was harder than normal. No intraabdominal masses could be felt.

Vaginal examination was essentially negative. Rectal examination showed a soft, round, smooth mass about the size of a plum in the anterior rectal wall, moveable upon the underlying tissues.

**Laboratory Findings.** The blood counts showed a slight anemia and a slight polymorphonuclear leukocytosis. The blood Wassermann, blood chemistry and urine examinations were all essentially negative.

**Roentgen-ray Findings.** The skull showed bone absorption in the posterior portion of the right frontal region and in the left half of the occipital bone. The spine showed no change. The left scapula showed destruction of the glenoid fossa and of the body adjoining it. The right showed slight absorption in the outer end of the acromion. There was a small amount of bone absorption in the middle of the shaft of the right humerus and a moderate amount of destruction of the heads of both radii. The left femur showed a small area of absorption at the upper and at the lower end of the shaft. The pelvis showed almost complete destruction of the descending ramus of the right pubis and the ramus of the ischium. The chest showed a dense, sharply circumscribed shadow, about 7 cm. in diameter in the left apical region with apparently complete destruction of the posterior portion of the fourth rib in this region. On the left side there was a large mass, 4 cm. in diameter, just outside the hilus glands. On the right side a fainter shadow extended from the level of the sixth to the eighth ribs to the axillary region with complete destruction of the eighth rib. There were a few small masses scattered throughout the right lung. The superior mediastinum showed a marked increase in width evidently due to an intrathoracic goiter. (Fig. 1.)

**Clinical Course.** There was gradual increase in the weakness, dysphagia, and dyspnea. The mass at the base of the neck and all the metastases showed progressive growth as demonstrated by palpation and by roentgen-ray studies. On August 31, 1924, the patient developed a flaccid paraplegia with clinical signs pointing to a level at the eighth dorsal segment. From this time onward the course was rapidly downward marked by distention, rectal and vesical incontinence and severe prostration with exitus on September 8, with a terminal pneumonia.

**Autopsy Findings.** Autopsy was performed one and a half hours after death by Dr. David P. Seecof who furnished us with the following report.

Body is that of a slenderly built, markedly emaciated, middle aged white woman.

*Abdomen.* Stomach and small intestine are negative. The colon presents several small nodules up to 1 cm. in size at the tips of the appendices epiploicæ, made up of grayish, translucent, congested tissue. In the anterior wall of the rectum, 8 cm. from the anus, is a globular mass about the size of a plum, lying between the muscular and the peritoneal coats and consisting, on section, of a grayish, translucent material.

*Pancreas.* Along the upper border are numerous grayish, globular, translucent bodies from 0.5 to 1 cm. in diameter.

*Liver.* On the anterior surface are several round, grayish, translucent tumor nodules, the largest 2 cm. in diameter, only slightly elevated above the general surface and not umbilicated. On section there are seen several nodules similar to the above from 1 cm. to 5 cm. in diameter, some showing a yellowish, central necrosis.

*Spleen.* Normal in appearance and consistency.

*Kidneys.* Many slightly elevated tumor nodules 2 mm. to 12 mm. in diameter, not adherent to the capsule, which on section are found to be similar to those in the liver. Pelves, ureters and vessels are normal.

*Adrenals.* Right: In the center is a grayish, globular, circumscribed translucent nodule 1.5 cm. in diameter. Left is negative.

*Pelvic Organs.* Bladder, uterus and ovaries are essentially negative.

*Chest.* Lungs, Right: Scattered throughout the depths of all three lobes are numerous globular nodules from 2 mm. to 5 mm. in diameter. Left: Projecting from the lower lobe at about the middle of the interlobar fissure is a globular mass 3 cm. in diameter. Near the lower part of the upper lobe immediately beneath the pleura are several nodules 1 cm. to 3 cm. in diameter. On section these nodules are all grayish, circumscribed and translucent.

*Heart.* The endocardium all over is smooth and glistening. Several small polypoid nodules are attached to the endocardial layer on and between the musculi pectinati, apparently not invading

the muscle layers. The largest of these, 5 mm. by 3 mm. by 2 mm. is situated near the tip of the auricular appendage; the smallest 2 mm. by 3 mm. in diameter, is almost completely hidden behind the muscle bundles. All appear as smooth, globoid, translucent bodies. One nodule 8 mm. in diameter is situated in the center of the interventricular septum, 2 cm. below the bases of the aortic leaflets (Fig. 2.)

*Neck Organs.* The esophagus, larynx and trachea are displaced to the right and their walls flattened although in no place infiltrated by the enlarged left lobe.

*Thyroid.* The right lobe is normal in size and situation, measures 3.5 cm. by 3.5 cm. by 0.7 cm. and weighs 5 gm. The isthmus is well formed and in its depths contains a hard, circumscribed nodule 1 cm. in diameter. The left lobe is roughly egg-shaped, measures 11 cm. through the poles, 6 cm. laterally and 7 cm. anteroposteriorly and weighs 120 gm. The lower two-thirds of its volume lay behind the clavicle and the first rib, the lower pole reaching the level of the first interspace 2 cm. to the left or the sternum. It is all over well encapsulated and not adherent to the overlying cervical tissues. Its surface is slightly lobulated and the consistency fairly uniform throughout. On section, the tissue is all over more or less translucent except for scattered irregular areas of opaque, yellowish, slightly granular necrosis. The nodule in the isthmus is a circumscribed translucent structure, not connected with the left lobe, made up of a densely fibrous and hyalinized capsule 1 mm. to 2 mm. thick, enclosing a small amount of dark semifluid material and foci of hyalinized fibrous tissue. Parathyroids are normal.

SKELETAL SYSTEM. *Ribs.* On the left side the medial portions of the second to the fifth and the seventh and eighth ribs are replaced by large, soft tumor masses. Some of these are situated at the junction of the ribs with the spine; others project into the thoracic cavity but in no place invade the parietal pleura. On the right side there are several small nodules on the inner surface of the upper ribs. On section, the masses in the ribs on both sides consist of hemorrhagic colloidal material of a granular nature.

*Vertebræ.* The third and fourth thoracic vertebræ are replaced by a large, soft, purplish mass extending 10 cm. to the left and posteriorly forming a prominent mass in the left paravertebral region.

*Scapulæ.* A large, soft, well encapsulated mass in the left axilla is found growing from the upper, outer angle of the left scapula. On section, it consists of a soft colloidal material similar to that in the rib metastases.

*Skull.* Underlying the prominent masses in the scalp in the right frontal and the left occipital region, tumor tissue similar to those in the ribs has completely replaced the bone and lies upon but does not invade the dura.

*Left Orbit.* Floating free in the orbital fat is a pinkish-gray, soft translucent mass, 3 cm. in diameter, not attached to the orbital walls, displacing the eyeball forward and lengthening and slightly thinning the optic nerve.

*Brain and Cord.* Near the medial anterior angle of the floor of the left middle fossa growing in the inner surface of the dura is a hard, globular mass 0.5 cm. by 1.5 cm. in diameter, which on section is found to be made of a yellow-white tissue. Brain is negative.

The tumor tissue adherent to the outer surface of the dura, at the level of the third and fourth thoracic vertebræ has not extended through this covering, although the cord in this region is thinned out and softened.

**Microscopical Examination.** *Thyroid.* The tumor, which is sharply differentiated from the neighboring normal tissue, consists of solid, interlacing columns of cuboidal cells with clear, vesicular nuclei, showing no alveolar differentiation. Some bloodvessels contain what appears to be normal colloid within their lumina; others show the presence of tumor cells interspersed with red blood corpuscles. (Fig. 3.)

*Lung.* The tumor mass completely replaces the normal lung markings, anthracotic particles within the tumor showing the remains of the original lung tissue. No differentiation into alveoli can be seen. (Fig. 4.)

*Heart.* Nodule is composed of small columns of cells similar to those in the thyroid, lying between the endocardium and the myocardium and sharply differentiated from both.

*Liver.* There is well marked differentiation into alveoli of various size containing colloid. These are scattered irregularly throughout the tumor mass, there being areas composed of undifferentiated solid strands of low columnar cells. (Fig. 5.)

*Pancreas.* Solid cell masses with no alveolar differentiation.

*Rectum.* Solid cell masses with an occasional suggestion of an attempt at alveolar differentiation.

*Kidney.* Metastases solid, same as lung, but largely necrotic. Where preserved, no alveolar differentiation can be observed.

*Dura.* Tumor shows considerable differentiation into alveoli containing colloid, but they are not as well shaped as those in the liver.

*Bone.* There is a definite attempt at alveolar formation, there being areas of various size and shape lined with low columnar cells and filled with a colloid like material.

**Comment.** As Balfour[3] has pointed out, a negative history does not rule out the previous existence of pathology in the thyroid gland. In only 1 of our cases was there a definite history of thyroid enlargement previous to the onset of clinical symptoms of malignancy. In the others it was impossible to establish the absence

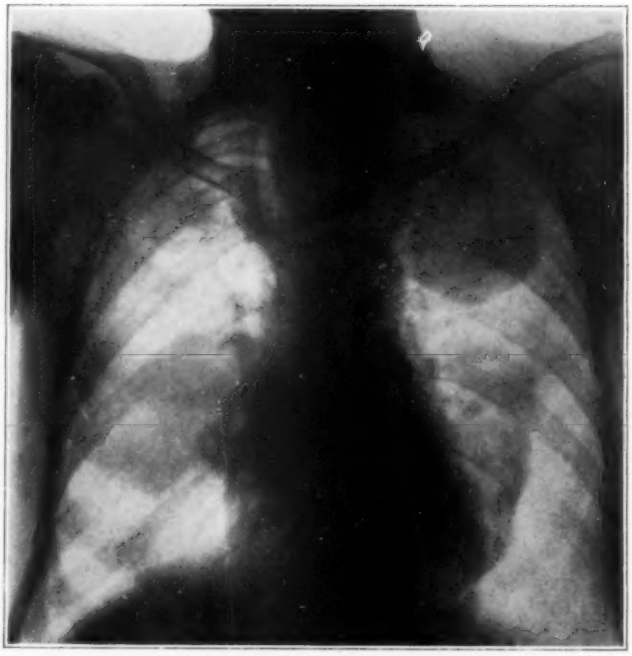

FIG. 1.—Roentgen-ray of chest showing large intrathoracic thyroid tumor and destruction of left fourth rib by mass in the paravertebral region. Smaller masses in the right apical region and in both hilus regions.

FIG. 2.—Heart showing small tumor nodules between the musculi pectinati in the auricular appendix.

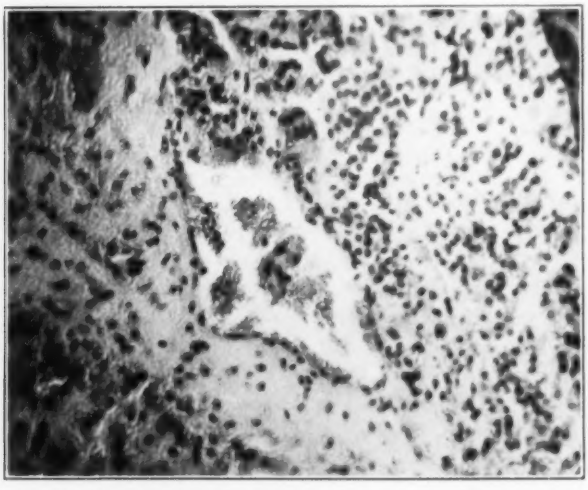

FIG. 3.—Showing the presence of an embolus of cancer cells within the lumen of a venule.

FIG. 4.—Showing extension of tumor cells through bloodvessel wall. This can best be seen at the upper right corner.

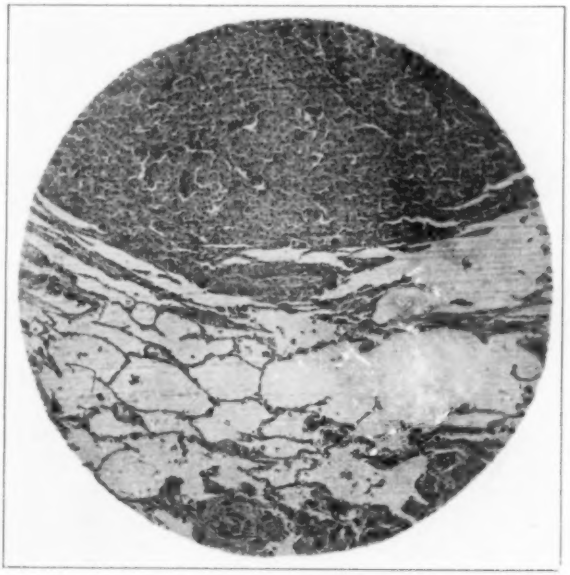

FIG. 5.—Nodule in lung showing the solid undifferentiated type of metastasis.

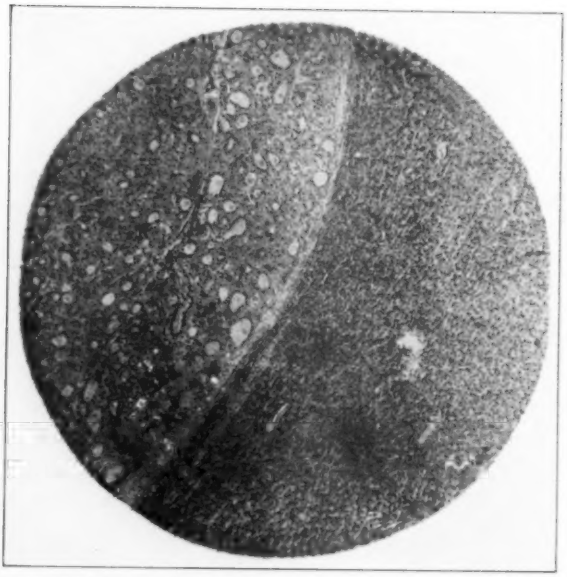

FIG. 6.—Metastasis in liver showing characteristic thyroid alveoli.

of a preceding lesion. In Case VII, particularly, in spite of careful questioning, no history of any enlargement of the neck preceding the onset of clinical symptoms of malignancy could be obtained, and yet, it is more than likely that the circumscribed nodule found in the isthmus, which seems to have given the first symptoms of the disease, had existed quiescently for a long time and that the patient had been made aware of its presence only when it had begun to undergo malignant growth.

Dysphagia, dyspnea and voice changes, all of which occurred early in 5 of our 7 cases, are due to local compression and usually form the first symptoms of the disease.

It is interesting to note that pain, which is usually looked for as an early diagnostic symptom, occurred early in only 1 of our cases, that local fixation occurred in all but 2 and that cachexia occurred in only 1 patient who had had a tracheotomy.

The exophthalmos noted in Case VII was entirely an incidental occurrence due, as autopsy subsequently showed, to a retrobulbar metastasis and in no way related etiologically to the type occurring in Graves' disease.

The occurrence of malignant change in abnormally situated thyroids has often been noted. Cases have been reported by Huguenin,[5] Greensfelder and Bettman,[7] de Graag[8] and others. Four of our 7 cases had intrathoracic thyroids. This comparative frequence of malignancy in aberrant thyroids is so striking as to suggest forcefully the possibility that abnormality of situation of the thyroid in some way predisposes to the development of malignant change, somewhat analogous to a similar predisposition noted in undescended testicles.

Paraplegia, as a complication of carcinoma of the thyroid, is uncommon. Cases have been reported by Huguenin, de Graag, Skversky and others. Its onset is, in some way, connected with the lodgment of metastatic emboli in the body of a vertebra, although at autopsy, there is seldom to be found any sign of cord compression. The direct cause of the paraplegia, whether it be chemical or neurotoxic in nature is, as yet, unknown. In Case VII, however, it was brought about in an unusual way by the extension of a metastasis, evidently in the left fourth rib, along the rib to the corresponding vertebra with its invasion and pressure upon the cord. Rather noteworthy is the long duration of the root pains—nine months previous to the onset of the paraplegia. It is also rather remarkable that the roentgenological evidence of spinal involvement was so slight that even when the paraplegia was well marked, the roentgenologists could not report any findings suggestive of any destruction of the vertebræ. This was probably due to the fact that the extrathoracic mass in the left paravertebral region effectually hid any pathology in the spine at the same level. This emphasizes forcefully the fact that especially in dealing with more than one shadow

in the same plane, the diagnostic powers of the roentgen-rays are not infallible and must, in a contingency, yield to clinical evidence.

The part played by trauma in determining the site of formation of metastases is problematical. Regensburger found 9 cases of cancer of the thyroid in which local trauma preceded the development of a metastasis. Kaufmann[9] mentions a case in which a metastasis seems to have developed on the site of a fracture of the femur. In Case VII, the history of trauma in the left occipital region three weeks previous to the development of a metastatic nodule in that situation, suggests the possibility of an etiological relationship between the two.

As to why metastases are numerous and almost ubiquitous in some cases (Case VII) and absent (Cases IV and V) or else confined to a solitary nodule in others, little explanation can be offered. Cohnheim[10] believed that their occurrence was determined by the individual resistance of the host. It is also somewhat difficult to explain the observation that metastases to the lung parenchyma, where they are believed to lodge first, usually remain small while the metastases in the bones grow rapidly. The explanation is probably bound up in the hypothesis that the lungs, in some way, offer poor soil for the development of this type of malignancy while the bones offer less resistance.

That cancer of the thyroid may metastasize by the blood as well as by the lymph stream was affirmed by Kaufmann as long as forty-five years ago. Recent studies have shown that hematogenous dissemination may occur in other types of cancer, but in carcinoma of the thyroid this mode of transmission is so frequent as to be almost the rule. The cause of this has not been explained. Possibly it is due to some peculiarity in the histological relationship between the bloodvessels and the acini in the thyroid gland. In Case VII there was no evidence whatever of any lymph-borne metastases, while beautiful evidence of dissemination by the blood stream was afforded by the occurrence of metastases in the ductless and other highly vascularized glands and by the actual demonstration of colloid and cancer cells in the bloodvessels of the primary tumor. The presence of metastatic nodules in the endocardium is an additional striking illustration of the same phenomenon.

The occurrence of metastases in the heart from a primary focus anywhere is very rare. Perlstein[11] mentions 19 cases of cancer of the heart in 9597 routine autopsies reported by Bryant in Baltimore and by Karrenstein in Berlin. Where the site is mentioned these all involved the pericardium or the myocardium; none occurred in the endocardium. Aschoff[12] mentions that cancer of the thyroid may metastasize to the heart and illustrates a melanotic tumor of the endocardium, but I could find no recorded instance of a metastasis to the endocardium from a primary carcinoma of the thyroid. The

rarity of cardiac metastases is probably due as Adami[13] has pointed out, to the fact that the heart, more than any other organ, is constantly in a state of efficiency, good nourishment and activity, hence does not allow the occurrence of aberrant growths.

Worthy of note is the occurrence of a different histological structure in the metastases in different situations, showing undifferentiated cell masses in the kidney, lung, etc., definite alveolar differentiation in the liver and the dura and an attempt at alveolar formation in the bones and to a lesser extent in the rectum. The cause of this differentiation is difficult to explain. It is not due to a difference in environment as was once thought, since different histological structure has been observed even on the same slide. Eberth thought that alveolar metastases in carcinoma of the thyroid represented a second generation, being produced by the primary metastases and thus forming a reversion to normal type, although Huguenin has pointed out that these alveolar metastases, in spite of their benign appearance, are actually more malignant than the solid type.

The question of the presence of function in metastatic tissue has long been the subject of dispute. As has been pointed out, it is only in cases of cancer of the thyroid that this can be determined since here only, in the characteristic power of thyroid tissue to pick out and fix iodin, have we a measurable criterion by which to estimate function. Ewald and Gierke claimed to have found iodin in metastases from carcinoma of the thyroid, thus tending to prove that they function as normal thyroid tissue. Marine and Johnson[14] however, in estimations upon 3 cases of thyroid carcinoma found practically none in the metastatic tissue and in estimations upon our Case VII, Dr. Marine was unable to find even a trace of iodin in the primary tumor or in the metastases, although the normal portion of the thyroid was found to be almost saturated with iodin.[15] These results point to an absolute absence of function in metastatic tissue and fall in well with our ordinary conceptions of the biology of a cancer cell.

**Treatment.** The present status of surgical treatment for malignant disease of the thyroid has been well summarized by Balfour who writes on the basis of an experience with 103 cases at the Mayo Clinic. In these, 70 per cent of the successful operations occurred in patients in whom the malignancy was an unexpected finding. When the disease is sufficiently well marked to make the diagnosis fairly definite the results of surgical treatment are discouraging. It is interesting to note in this connection, the apparent cure in Case V, by operation performed one year after the clinical onset of the disease. Radiotherapy seems to be of some value in inoperable cases and as an adjunct to the surgical treatment.

**Summary.** Seven cases of malignant tumor of the thyroid are analyzed—1 sarcoma and 6 carcinomata. Of these, 1 patient

shows healing of a spontaneous fracture from a metastasis from a sarcoma of the thyroid and is alive and about his work three and a half years after the clinical onset of the disease. Another, after a lobectomy performed one year after the clinical onset of the disease is apparently well with no sign of recurrence two years after the operation. One patient showed an unusually wide distribution of the metastases and developed a paraplegia. At autopsy this was found to be due to a metastasis lodged in the vertebral column as an extension process from a metastasis in the rib. This had caused definite vertebral destruction and cord compression, but did not show up on the roentgen-ray plate during life. In this case, there was no evidence clinically or pathologically of any lymphatic dissemination. Hematogenous dissemination was illustrated by the actual demonstration of cancer cells in smaller bloodvessels of the primary tumor and by the presence of metastases in the endocardium. The latter is a rare finding. No similar case has been found in the literature. The metastases in the different organs showed a different histological structure with reference to the presence or the degree of alveolar differentiation. No evidence of function as determined by the power to fix iodin could be found either in the primary tumor or in the metastases.

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# THE KOTTMAN REACTION IN THYROID DYSFUNCTION.:

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To attempt to define the various types of thyroid dysfunction, using the clinical picture alone, is often confusing. Classification should be made on the basis of criteria much more definite than physical signs yield. Otherwise, we may have endless discussion that leads to conclusions anything but conclusive. As laboratory methods advance and progress, however, we begin to see in them the solution to this problem.

Thyroid dysfunctions now may be studied by any of the following methods: (1) Basal metabolism; (2) Goetsch test (adrenalin); (3) serologic tests for thyroid secretion. The first two methods we will not consider in detail. Of serologic tests, we may have two kinds: (1) The complement-fixation reaction; (2) the Kottman test.

The purpose of our studies was to discover whether we could get positive results in known thyroid cases when using the Kottman test, and in addition to see how the results of this test compared with those of basal metabolism.

**Principles of the Test.** This test, evolved by Kurt Kottman of Switzerland, is based on a two-fold theory: (1) That one colloid has a protective property for another colloid; (2) that a photosensitive substance reacts more to the light in fine suspension than in coarse suspension.

When silver nitrate is added to potassium iodid in the presence of human serum, the result is a cloudy mixture. There has been formed silver iodid, wich is held in colloidal suspension by the serum which is itself a colloid. In sera, the protective power for another colloid varies. It is strongest in hyperthyroid serum, weakest in hypothyroid serum and intermediate in normal serum. In other words, the suspension of AgI in hyperthyroid serum is very fine, less fine in normal serum and relatively coarse in hypothyroid serum. Now, when the colloid is exposed to the light and the developer (in this case hydroquinon) is added, the reduction to metallic silver varies inversely with the fineness of the particles in the suspension. Therefore the change from AgI to metallic Ag is greatest in the hypothyroid serum, and least in the hyperthyroid serum. Since this chemical change is evidenced by a change to a brownish color, we have a simple index to the degree of secretion. In hyperthyroidism there is little change in color, in hypothyroidism the color changes fairly rapidly to a brown that is almost black, while in normal serum, the change comes half-way between these two extremes.

**Technique.** 1. Five cc of blood is withdrawn from the vein by the usual method.

2. The blood is centrifugalized to obtain the clear serum.

3. To 1 cc of clear serum is added 0.25 cc of potassium iodid solution (0.5 per cent) and 0.3 cc of silver nitrate solution (0.5 per cent).

4. Mix thoroughly and carefully by shaking.

5. The colloidal suspension of silver iodid formed by this mixing is exposed for fifteen minutes to a 500-candle power light held at a distance of 25 cm.

6. To the suspension is added 0.5 cc hydroquinon (0.25 per cent) solution.

7. Readings are taken every five minutes for thirty minutes. For convenience, we grade the color changes from zero to 4+.

These are the only conditions which are absolutely essential. There are others, however, which if observed, make for greater accuracy, and so reduce the possible sources of error. The best and most reliable results are obtained when the patient has fasted for twelve hours before the blood is taken. Bromids used within two months before the time of the test will retard the reaction. Should the patient have taken bromids, due consideration should be given this fact in noting the result. The blood should be used as soon as possible after it is withdrawn. It is best to add the KI and the $AgNO_3$ in a dark room using a red light. This same precaution should be observed when the hydroquinon is added to the AgI. And last, but by no means least, blood serum from a normal individual should be used as a control.

**Interpretation of Readings.** From our studies and our observation of what we assumed to be normal cases, we considered a normal reaction one in which there are some evidence of color change within the first five to ten minutes and then a gradual deepening of this color to a definite dark brown within thirty minutes. When there is hypersecretion the reaction or color change is considerably retarded. At first there may be no apparent change. Even at the end of the prescribed period of observation there may be only a slight darkening. When the change comes quickly and there is a brownish discoloration in the first five minutes, this color rapidly becoming darker until it approaches black, we consider that here we have deficiency of thyroid secretion.

**Discussion.** Our studies with the test were made in three groups: (1) Hyperthyroid cases; (2) hypothyroid cases; (3) general conditions. This last group was included to determine how the Kottman test results compared with the readings of the basal metabolism tests.

Unfortunately, our thyroid case material was not so extensive as others, who have worked with this test, have reported. Out of 100 cases there were available only 14 patients who were observed for the effect upon goiter and hyperthyroidism.

TABLE I. THYROID CASES.

| No. | Name. | Thyroid. | Von Graefe. | Tremors. | Basal metab. | Kottman reaction, minutes. | | | | | | Result. | Remarks. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 5 | 10 | 15 | 20 | 25 | 30 | | |
| I | F. P. | Enlarged | Present<br>+ | Absent<br>○ | +13 | + | + | + | ++ | ++ | +++ | Slight retarded | A previous reading was +24. |
| II | M. L. | Palpable | ○ | + | +14 | ○ | + | + | ++ | +++ | +++ | Slight retarded | |
| III | E. T. | Enlarged | + | + | +54 | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | Retarded | |
| IV | M. S. | Enlarged | + | + | +20 | ⊕ | + | ⊕ | ⊕ | + | ++ | Retarded | |
| V | I. R. | Enlarged | + | + | +25 | ⊕ | + | + | + | + | ++ | Retarded | |
| VI | M. M. | Enlarged | + | ○ | +20 | ⊕ | ⊕ | + | + | + | + | Retarded | |
| VII | A. M. | Enlarged | ○ | ○ | +14 | ⊕ | ⊕ | + | + | ++ | ++ | Retarded | |
| VIII | M. J. | Enlarged | + | ○ | +51 | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | Retarded | A previous reading was +75. |
| IX | A. G. | Enlarged | + | + | +18 | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | Retarded | |
| X | I. E. | Enlarged | + | + | +19 | ○ | ○ | + | + | + | ++ | Retarded | |
| XI | C. B. | Enlarged | + | + | +21 | + | ++ | ++ | +++ | ++++ | ++++ | Normal | Unexpected reaction. |
| XII | M. B. | Palpable | + | ○ | +18 | ○ | ○ | + | + | + | ++ | Retarded | |
| XIII | F. P. | Enlarged | + | ○ | +21 | + | + | + | + | ++ | ++ | Slight retarded | |
| XIV | R. O. | Palpable | + | ○ | +18 | ○ | ○ | ○ | ⊕ | ⊕ | ⊕ | Retarded | |

○ = no color change.
⊕ = doubtful.
\+ = light brown.
++ = brown.
+++ = dark brown.
++++ = black (or a very dark brown.)

I should mention that these were not necessarily early cases of exophthalmic goiter. Case I, for example had an enlarged thyroid, with exophthalmos. There were no tremors of the outstretched hand. The patient was operated upon two years before when part of the thyroid was removed. The metabolic rate was +13, which is only a slight elevation above the normal limit. The Kottman test showed a slightly retarded reaction.

With the exception of C. B., No. XI, the blood test tallied with the basal metabolism results. Here (C. B. No. XI) we are dealing with a frank exophthalmic goiter of one year's duration. The patient is a white female, aged twenty-nine years. Despite constant medical care and roentgen-ray therapy, her condition had progressed with the usual effect upon the heart. The patient's condition was so poor that I hesitated to make any blood studies that might excite her. After the exophthalmos subsided, the damaged heart was beyond repair. The goiter, von Graefe, and tremors still persisted. It was at this time that the Kottman test was performed. The result was, surprisingly, a normal reaction. This reading may be looked on in two ways. The first instinct is to feel that the test has failed. On the other hand, we may consider that our knowledge of the thyroid being still incomplete, it might be possible that an overactive gland ceases to throw off excessive amounts of thyroid secretion. Occasionally we do see cases in which there is a swing from a state of hyperactivity to deficient secretion of thyroid substance. If this is true, then the Kottman has an added value because it gives us information of the gland's activity which we do not, as in this cited case, get from the misleading clinical picture.

D' Houbler, in a series of 58 cases of exophthalmic goiter, had a similar experience. In all but 1 of his cases, the Kottman reaction indicated a state of excessive secretion. In the exceptional case, there was seen an accelerated reaction such as we find in hypothyroid cases.

Peterson and his coworkers, in a series of 70 cases, found the test lacking in only 3 instances. In 1 case there was an accelerated reaction and in the other 2, normal reactions.

*Hypothyroid Group.* Two patients with definite evidences of hypothyroidism were studied with the following results:

| | Thyroid. | von Graefe. | Tremors. | Basal. | Kottman. |
|---|---|---|---|---|---|
| I T. D. . . . . | Not palpable | 0 | 0 | −20 | ++++ |
| II S. B. . . . . | 0 | 0 | 0 | −14 | ⊕⊕⊕⊕ |

The first case showed a markedly accelerated reaction, such as we might expect in this condition. Case II who was admitted as a case of myxedema, showed a retarded reaction. This unexpected result might be explained by the fact that this patient had been treated with thyroid substance for several days prior to the taking

TABLE II. A COMPARISON BETWEEN THE READINGS OF THE KOTTMAN TEST WITH THE BASAL METABOLISM IN MISCELLANEOUS CONDITIONS.

| No. | Name. | Evidence of thyroid dysfunction. | Basal metab. | Kottman reaction, minutes. | | | | | | Result. | Diagnosis. | Remarks. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 5 | 10 | 15 | 20 | 25 | 30 | | | |
| I | R. G. | None | +9 | + | ++ | ++ | +++ | ++++ | ++++ | Normal | Cardiac | |
| II | D. P. | Exophthalmos | +8 | + | ++ | ++ | +++ | ++++ | ++++ | Normal | Pneumonia | (Convalescing). |
| III | R. A. | None | +1 | + | ++ | ++ | +++ | ++++ | ++++ | Normal | Neurasthenia | |
| IV | J. G. | Slightly enlarged thyroid; coarse tremors | +10 | ⊕ | + | ++ | ++ | +++ | ++++ | Normal | Vasomotor ataxia | |
| V | A. S. | None | +6 | + | + | ++ | +++ | ++++ | ++++ | Normal | Nephritis | |
| VI | R. O. | Von Graefe, tachycardia | +64 | ○ | ○ | ○ | ⊕ | ⊕ | ⊕ | Retarded | Psychasthenia | |
| | | After 3 weeks rest | +18 | ⊕ | ⊕ | ⊕ | + | + | ++ | Retarded | | |
| VII | A. C. | None | +10 | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | Retarded | Tachycardia | (Presumably of endocrine origin). |
| VIII | N. R. | None | +4 | + | + | + | + | + | + | Retarded | Lipomatosis | (Symmetrical). |
| IX | G. D. | None | +17 | ++ | ++ | ++ | +++ | +++ | ++++ | Normal | Diabetes | |
| X | S. E. | None | +9 | + | ++ | +++ | ++++ | ++++ | ++++ | Normal | Diabetes | |
| XI | B. H. | None | +8 | + | ++ | ++ | +++ | +++ | +++ | Normal | Diabetes | |
| XII | M. V. | Tremors | +30 | ++ | +++ | +++ | ++++ | ++++ | ++++ | Slightly accelerated | Diabetes | |
| XIII | S. E. | None | −1 | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | Retarded | Diabetes | High-strung. |
| XIV | M. J. | Slightly enlarged thyroid tremors | +19 | + | + | ++ | ++ | ++ | +++ | Slightly retarded | Diabetes | Very high-strung. |
| XV | S. W. | Palpable thyroid, no toxicity | +21 | + | + | + | ++ | ++ | +++ | Slightly retarded | Diabetes | |
| XVI | S. Z. | Von Graefe | +11 | + | + | + | + | + | + | Retarded | Diabetes | Hypertension. |
| XVII | A. G. | None | +14 | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | Retarded | Diabetes | Hypertension. |
| XVIII | S. B. | Slightly enlarged thyroid | +11 | ⊕ | ⊕ | + | + | + | + | Retarded | Diabetes | |
| | | | | | | | | | | Accelerated | Nephritis | |
| XIX | T. D. | None | −20 | +++ | +++ | ++++ | ++++ | ++++ | ++++ | | | |
| XX | S. B. | None | −14 | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | Retarded | Myxedema | Thyroid gland had been given. |

of blood for Kottman reaction. Although we knew of this, we were curious to discover what the result would be under the circumstances.

The retarded reaction was quite possibly due to the excessive amount of thyroid substance present in the blood stream as the result of the thyroid administration. Peterson and colleagues noted this same fact when in their experiments with dogs, they administered thyroxin.

**Comparative Study of Basal Metabolism.** *Tests with Kottman Reaction.* Table II was arranged to show how the Kottman reaction results checked with metabolic readings in order to determine how reliable a test the former may be considered. Of the 20 cases tabulated in Table II, we find four discrepancies between the two results (Nos. IX, XII, XIII, XX). Table I shows one other, Case No. XII—C. B. The total number of cases, then, where we find no check between the two tests, is 6, out of the total of 34 cases which were studied. It would be unfair to the Kottman test to condemn it for these failures without first giving due consideration to certain aspects of each of these cases.

Case IX, G. D., clinically showed no evidence of thyroid dysfunction, yet the basal metabolic rate was +17.

Case XII, M. V., likewise showed +30 with no other manifestation than tremors.

Case XIII, S. E., a high-strung individual with a definitely retarded Kottman reaction indicating hypersecretion, showed a −1 basal rate.

These patients, it should here be noted, were all diabetics.

The remaining 2 cases, No. XX, S. B., diagnosed myxedema, and No. XII, C.B. (Table I), diagnosed exophthalmic goiter, have already been discussed.

Reviewing these cases and taking into consideration the clinical picture, it seems unfair to use as evidence against the Kottman reaction, the failure of Nos. IX, XII, XIII to coincide with the metabolic result. It is possible that these very discrepancies might indicate the repeating of the basal metabolism test to confirm the first readings. The case for the Kottman reaction might have been made stronger if these confirmatory tests had been done. It is unfortunate that this was not done, for the personal equation enters so largely into the metabolism test that quite possibly we could have gotten results more compatible with the Kottman results. So often the technician, conducting the metabolic studies, is hampered by either the lack of intelligence, or by the nervousness of the subject. Despite all the precautions, these factors may bring about a higher reading. If we accept these in considering our results we may, then, narrow down the number of discrepancies to 2 cases in the miscellaneous table and 1 in the thyroid table which is by no means a poor showing for the still unrecognized Kottman reaction.

When we reach the point where we can definitely say that this

test is reliable, its advantages over the basal metabolism test can easily be demonstrated. The technic which is simple, calls for no expensive or cumbersome apparatus. The unreliable element of the patient's emotional state or temperament cannot influence the result. It may be used for those patients who cannot be moved. Unmanageable patients or those without teeth to grip the mouthpiece of the metabolic apparatus, can be tested in this way without undue annoyance to either patient or physician.

**Conclusions.** From our studies with the Kottman reaction and from a comparison of its results with that of the basal metabolism tests, we feel that this method of measuring the degree of thyroid secretion can be said to be of value. We found, with our limited material, that the test is consistent (with only an occasional exception) in thyroid dysfunction (particularly hyperactivity). We found also that, except in a few cases, our test checked up with the basal metabolism results.

This test, if recognized as proven, would be valuable for the following reasons:

It is simple in its technique and apparatus.

It would be a very good substitute when basal metabolic readings are not so easily obtained.

It would, because of its simplicity, be an excellent measure for checking results obtained by the basal metabolism test.

Unless this test can be shown to be absolutely inaccurate and worthless, I believe it should be given a fair trial. Sufficient studies have not yet been made to permit us to decide whether it should rank with such proven tests as basal metabolism and the Goetsch test. I think that it has merit enough to warrant its being used in clinics where there is abundant thyroid material. It is only in this way that its reliability can actually be determined and its value proved.

I wish to express my thanks to Jacob Wollen who assisted me in collecting experimental data for this study.

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# FURTHER STUDIES OF CEREBROSPINAL FLUID IN INFANTS AND YOUNG CHILDREN.*

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**Normal Infants and Children.** For comparison with the data furnished by lumbar puncture in various diseases, the following will be considered as normal cerebrospinal fluid—clear and colorless, slightly alkaline in reaction, specific gravity approximating 1002. Pressure is disregarded in the age group under consideration as it is greatly influenced by crying and muscular movements, and these cannot be controlled in infants. Globulin does not exist in demonstrable quantities in the normal cerebrospinal fluid of infants; when a definitely positive globulin reaction is present the fluid is pathological. Lymphocytes are normally the only cells present in cerebrospinal fluid; as many as 20 per c.mm. may be found in a normal child.

There is nearly always a positive reaction for a reducing substance, dextrose, which varies in amount as determined by the Folin and Wu method, between 45 and 85 mg. per 100 cc of fluid.

The chlorids are so variable, 600 to 750 mg. per 100 cc of fluid, that any constant relationship in their amount to any of the meningeal or extrameningeal infections has not been determined by us.

**Cerebrospinal Meningitis.** Thirty-five cases of cerebrospinal meningitis are presented, 23 of which were proved by the isolation of the meningococcus from the blood or cerebrospinal fluid and 12 by the clinical course and response to specific serum therapy in addition to changes in the cerebrospinal fluid. Many of these patients were admitted in a moribund condition. Eleven were discharged from the hospital cured of the condition for which they were admitted, 7 were improved and 17 died, of which 3 came to autopsy.

These cases were from one month to four years of age, 13 were not over six months of age and 25, or 71 per cent, were not over one year of age. This is a striking commentary on the age incidence of the sporadic type of meningococcus infection. It seems probable that because of the mild character of the symptoms in many cases in infancy a number of such infections remain unrecognized. In not a single instance was a clear fluid obtained by the first

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lumbar puncture, although in 4 instances the cell count was less than 500 per c.mm. One specimen of fluid from which meningococci were obtained contained only 100 cells, yet was slightly turbid due to fibrin. In most instances the fluid was described as turbid, but in 2 patients with counts over 10,000 it was frankly purulent in character. In a few cases the globulin test was not recorded. In all the others it was positive.

In 29 cases in which a qualitative test for sugar was done it was negative in 24 cases, faintly defined in 1 and in 4 cases definitely positive. Since the meningococcus possesses the power of fermenting glucose it naturally follows that a diminution of the sugar content of the cerebrospinal fluid should be noted in the cases with moderately increased cell counts and a complete absence in the fluids with high cell counts, particularly those with purulent fluids. Along these lines the following may be of interest. In cerebrospinal fluid from 16 patients a quantitative estimation of sugar was made. In the first or second lumbar puncture made after admission to the hospital the fluid in 4 cases contained no sugar, 7 had not more than 26 mg. per 100 cc of fluid and of the remaining 5 cases, 4 were not above 45 and 1 only had a normal content of 65 mg. per cc, which was late in the disease when the cell count was only 110 and the culture showed no growth. These patients were admitted to the hospital during various stages of their infection. It is of interest to note the rise of the curve of sugar, as the number of cells diminish with specific serum therapy.

**Case Reports.** CASE I.—Patient (25,121), aged four years, is typical. From the first lumbar puncture cloudy fluid was withdrawn which contained 3000 cells per c.mm. and numerous meningococci. The sugar quantitatively was 20 mg. per 100 cc. Specific intraspinous and intravenous serum therapy was commenced immediately, and during the period of hospitalization the sugar was determined quantitatively eight times. There was a gradual rise in the sugar content coincident with the decrease in the number of cells. At the eighth lumbar puncture the cell count had diminished to 36 cells and the sugar had increased to 58 mg. The patient was discharged cured.

CASE II.—E. A. (23,558), aged eighteen months, with 4460 cells and 28 mg. of sugar per 100 cc, showed meningococci in both blood and cerebrospinal fluid; 10 cell counts were made during the period of treatment, at the last puncture but one only 9 cells were present and the sugar had increased to 59 mg. per 100 cc of fluid. The patient was discharged cured.

Of special interest is T. B., Case 24,437, aged one month, who had two lumbar punctures and two cistern punctures while under

observation. In the first puncture 2620 cells were counted and the sugar content was 39 mg. per 100 cc of fluid. No response to serum therapy was observed, and therefore only a slight diminution in the number of cells occurred. The sugar decreased before death to 18 mg. per 100 cc of fluid and the cell count was 1960.

**Encephalitis.** Nine cases of encephalitis are presented, from six months to five years of age, all but one of whom were discharged as improved of the condition for which they were admitted. In only 5 cases was pleocytosis present; the highest cell count on admission was 220. In 5 of the cases a faint globulin reaction was present. The only constant finding of interest in these cases was a high sugar content, which was noted in 4 of 6 cases in which the chemistry was done. In the other 2 cases the quantitative sugar was in the upper limit of normal. The two following cases are of special interest on account of the chemistry.

CASE III.—T. S. (24771), aged eighteen months, was admitted because of vomiting, drowsiness, rigidity of the neck and convulsions. At the initial puncture clear fluid was withdrawn which showed 220 cells, 80 per cent of which were lymphocytes. The globulin test was negative, and the test for a reducing substance was positive; 108 mg. of sugar per 100 cc was present. Successive counts showed 120, 150, 154 and 37 cells respectively. Successive sugar estimations were 108, 99, 62 and 27 mg. per 100 cc of fluid, which demonstrates very nicely the decrease of the sugar with the disappearance of the evidence of meningeal irritation. The last sugar determination was much below normal, and was obtained from a fluid showing only 37 cells. The patient was discharged cured.

CASE IV.—B. T. (25485), aged three years, showed a persistently high sugar throughout the course of her disease which terminated fatally. She was admitted on account of drowsiness, slurring speech, anorexia and convulsions. She was comatose on admission and remained so during the twelve days' period of observation. The first cerebrospinal fluid obtained was from a cistern puncture. This showed 160 cells with a predominance of polymorphonuclears, a trace of globulin was noted and the test for a reducing substance was positive. The quantitative test for sugar gave 105 mg. per 100 cc of fluid. Four other specimens of cerebrospinal fluid all obtained by lumbar puncture showed only 108, 30, 1 and 2 cells respectively, yet the sugar remained constantly high, 89, 92, 102. The temperature had daily fluctuations between 101° and 105.6°, once reaching 106° F. An autopsy which was performed, December 25, 1924, showed a rather friable brain with no inflammation of its coverings. (It is now in a hardening solution in preparation for further study.)

A predominance of the polymorphonuclear cells in the cerebrospinal fluid of this case may be explained by the fact that the first stage of encephalitis, like the first stage of poliomyelitis, is accompanied by a meningeal irritation which means polymorphonuclear cell increase. A marked leukocytic reaction of the blood in 6 of 7 cases, with an average of 19,600, may be worth recording, but it would not serve as an aid in differential diagnosis since all infections of the central nervous system may at some stage be accompanied by a high white blood cell count.

**Encephalitis Due to Lead Poisoning.** The following three cases of encephalitis due to lead poisoning seem of sufficient interest to merit attention, especially since poisoning by lead is seldom considered as a diagnostic possibility in infants and young children. These cases will be reported in detail by Dr. F. G. Beal.

CASE V.—R. G., aged four and a half months, was nursed from birth, and thrived until three weeks before admission to the Babies' Hospital. Irritability was then noted, vomiting occurred frequently and eventually twitching of the right arm and the right side of the face was observed. On admission, twitching of the right arm was observed in addition to a bulging fontanel and exaggerated knee jerks. Fever was not present. Routine examination of the blood disclosed marked basophilic stippling of the red cells, and on more complete investigation it was learned that the mother had used lead nipple shields for both breasts since her discharge from the maternity hospital. Lead was found in the mother's milk and in the stools of the infant. The first lumbar puncture showed a clear fluid with 60 cells, a trace of globulin and positive sugar reaction. The third lumbar puncture showed turbid fluid, the first part withdrawn was slightly blood tinged. It contained 70 cells, 80 per cent of which were polymorphonuclears. The reaction for globulin was marked. (Bloody fluids are in nearly every instance discarded at the Babies' Hospital.) The quantitative sugar determination showed 46 mg. per 100 cc. The chlorids were 738 mg. The third puncture showed turbid fluid with 1130 cells, 93 per cent of which were polymorphonuclears. The reaction for globulin was marked. No lead was discovered in the spinal fluid. The infant was discharged cured.

CASE VI.—H. L., a child, aged sixteen months, died after a brief period of observation in the Babies' Hospital. Basophilic stippling of the red blood cells drew attention to the fact that lead poisoning was probably present. The infant's father was a painter; other than this no source could be discovered for the presence of the lead. The organs were removed at autopsy and lead was demonstrated. Only one lumbar puncture was done, which showed 16

cells and a positive globulin reaction. The qualitative reaction for sugar was negative.

CASE VII.—S. K. (24,663), a defective child, aged twenty months, was admitted to the hospital with the statement that for two months he had had a perverted appetite, had eaten paint off furniture, bits of paper, etc. For two weeks vomiting had been noted, which just prior to admission became projectile in character. Drowsiness had been present for a day. This child succeeded in eating considerable amounts of freshly applied enamel from his bed during his early period of hospitalization. Basophilic stippling of the red blood cells was noted. On lumbar puncture a clear fluid was withdrawn which showed 22 cells, 74 per cent of which were polymorphonuclears. The globulin reaction was strongly positive. The quantitative sugar determination was 52 mg. and the chlorids 713 mg. per 100 cc of fluid. Four days later clear fluid was withdrawn by lumbar puncture which showed 26 cells—all lymphocytes. The reaction for globulin was positive. A later puncture showed clear fluid with 15 cells—mostly lymphocytes. The globulin reaction was positive. The spinal fluid had 72 mg. of sugar per 100 cc and 675 of chlorids. The last lumbar puncture showed only 4 cells and 62 mg. of sugar. Lead was found only in his stools. He was discharged improved.

**Acute Poliomyelitis.** Lumbar puncture was done in 7 cases of poliomyelitis and polioencephalitis, with an average age of nineteen and a half months. Several of these cases were admitted to the hospital a number of days after the acute symptoms had subsided, which accounts for the negative findings in the cerebrospinal fluid. All were discharged improved of the condition for which they were admitted. In the 7 cases the fluid withdrawn was clear and colorless, and in 3 cases only were more than 20 cells found. In 5 cases in which a test for globulin was done it was positive in 4. The test for a reducing substance was positive in the 6 cases in which the test was done.

Chemical analysis for sugar was done in 6 of the 7 cases and showed the amount to be within the normal limits in all. In 4 cases in which a quantitative determination of chlorids was done all were within normal limits.

CASE VIII.—F. M. (23,857), aged nineteen months, who had five different chemical analyses for sugar and chlorids, is an example of the variability shown in the chemistry of the cerebrospinal fluid in this condition. The patient was admitted because of vomiting, irritability and drowsiness, and at the onset and for several days thereafter the working diagnosis was tuberculous meningitis. Lumbar puncture showed clear fluid at each tap with 15, 5, 24, 14 and

4 cells respectively. The globulin test was positive in two out of four examinations. No organisms were obtained by smear or culture of the cerebrospinal fluid. The quantitative determination of sugar gave the following values per 100 cc of fluid: 71, 76, 62, 50, and 101. Four were within normal limits, with one in the lower zone of normal, while one was considerably above normal limits. This child was discharged improved of the condition for which he was admitted.

From the evidence here presented in a small group of cases with chemical findings, and confirmed by earlier observations of a large group of cases without chemical analyses, the only changes in the cerebrospinal fluid which will aid in the diagnosis in the acute stage of the disease is a cellular reaction and a positive globulin reaction.

**Tuberculous Meningitis.** Nineteen cases of tuberculous meningitis are presented, from seven months to five and a half years of age, with an average age of twenty months. In 16 cases the diagnosis was proved either by autopsy (in 9 cases) or by the discovery of tubercle bacilli in the spinal fluid. In 3 cases the diagnosis was made on the history, the course of the disease in conjunction with the result of the Pirquet test and the findings in the cerebrospinal fluid. In 13 cases tubercle bacilli were found in the spinal fluid. This is a lower percentage of positive fluids than the general results at the Babies' Hospital, to be explained by the short period many of these cases were in the hospital, thus allowing of but one examination of cerebrospinal fluid. No tubercle bacilli were found in the cerebrospinal fluid of Case 25117. At autopsy only recent tubercles were present along the vessels and no fibrinous exudation, which explains the absence of organisms in the cerebrospinal fluid.

Although in several instances more than 300 cells per c.mm. were counted, in every one of the 19 cases the fluid was clear and colorless.

There is an impression, which is a correct one, that lymphocytes are the predominating cell in the cerebrospinal fluid of tuberculous meningitis, especially in the early stages, and that polymorphonuclear leukocytes frequently predominate in the last stage. However, in the 15 cases in this series, in the fluid from the first lumbar puncture lymphocytes predominated in only 6, while in 7 the polymorphonuclears were in excess and in 2 cases the cells were equally divided. Many of the patients in this group were admitted in the later stages of the disease.

There is a wide variability in the number of cells; several cases presented low cell counts, 2 were less than 50 cells and the highest count in any of the 19 cases was 1260 cells.

The cellular reaction seems to bear no relationship to the num-

ber of tubercle bacilli in the cerebrospinal fluid. In 1 case with a cell count of but 20 tubercle bacilli were discovered on the first examination, while in 2 cases, proved by autopsy each with more than 300 cells, tubercle bacilli were not discovered in the cerebrospinal fluid.

In several cases repeated puncture in various stages of the disease failed to reveal a marked cellular reaction. Case 24662, proved at autopsy, showed 28, 84, 30 and 40 cells in four successive lumbar punctures. In 18 of the 19 cases on which a test for globulin was made it was definitely positive in all, and in 13 the reaction was very marked. In 18 cases in which a qualitative test for a reducing substance was done it was positive in 8 cases, faintly positive in 1 and absent in 9.

A quantitative estimation of dextrose was done in 13 cases, 12 of which were proved by autopsy or by the finding of tubercle bacilli in the spinal fluid. In only 1 of the cases was the sugar normal; in 12 it was definitely reduced, of which 3 showed the sugar content to increase toward the terminal stages. The highest dextrose content per 100 cc of cerebrospinal fluid was 75 mg. Several specimens were examined which contained no sugar. The average for the cases in which a quantitative sugar determination was made was 28 mg. per 100 cc. It is thus apparent that there is a definite diminution of dextrose in tuberculous meningitis, which should at least serve as a help in the early differential diagnosis between this disease and encephalitis. It has been maintained by some that the chlorids are diminished, but in the 12 cases in which a quantitative determination of chlorids was made the variability was so wide there is little evidence of any diagnostic value in a chlorid determination. Only extremely rarely at the Babies' Hospital* has a case of tuberculous meningitis came to autopsy in which general miliary tuberculosis was not demonstrated at the autopsy table. In 8 of the 9 autopsies in this series tuberculosis of the meninges was found to be only one lesion of a general miliary tuberculosis.

**Pneumococcus Meningitis.** In 5 cases of pneumococcus meningitis pneumococci were demonstrated in the cerebrospinal fluid. In 3 of the 5 cases organisms were also found in the blood stream. All of the 5 patients died. The youngest patient was three months of age and the oldest was twenty-nine months. All the specimens of fluid, as would be expected, were turbid, and the average count for the first lumbar puncture taken on admission to the hospital was 980 cells. In every case the globulin was strongly positive. The quantitative test for sugar was similar to the other purulent types of meningitis, that is, consistently low. The average for five examinations showed only 26 mg. per 100 cc of fluid. The average chlorid content for four examinations was 617.

* Wollstein and Bartlett; Am. Jour. Dis. Child., 1914, **8**, 362.

**Congenital Syphilis.** Sixteen infants are listed under this diagnosis—from five weeks to twenty-seven months of age; 6 were under six months. In 7 cases the diagnosis was made on the blood Wassermann reaction alone. In the others, all of whom had positive blood Wassermann tests, it was made either at autopsy (in 5 cases), by florid cutaneous manifestations or by a positive Wassermann of the cerebrospinal fluid. In 13 cases in which the globulin test was done it was positive in 6, faintly positive in 1 and negative in 6. The average cell count, excluding the case of syphilitic meningitis, was 30 per c.mm. Five of 15 cases had an increased number of cells. One infant, with clinical syphilis and a 4+ blood Wassermann reaction, gave a negative globulin test in the spinal fluid. Another clinical case, with 27 cells in the cerebrospinal fluid and a positive blood Wassermann reaction, did not show any globulin in the spinal fluid, but a third case, with a positive Wassermann reaction in the blood and in the spinal fluid, in three examinations gave a negative globulin reaction in one specimen of fluid and extremely faint reactions in two other specimens.

Of 11 patients, all with positive blood Wassermann tests, in whom the diagnosis was made by marked clinical manifestations, by a spinal fluid Wassermann test or by autopsy, only 5 showed an increased number of cells in the spinal fluid—28, 160, 162, 27, and 504 cells, respectively.

It was noted in a previous study of a larger group of cases, and again in this group, that congenital syphilis may involve the central nervous system without showing an increase in the number of cells in the cerebrospinal fluid.

The following case illustrates this point:

Case IX.—R. C. (24,732), aged eighteen months, was admitted because of drowsiness, muscular weakness and convulsions. The blood and cerebrospinal fluid gave a 4+ Wassermann reaction and 66 mg. of sugar per 100 cc of spinal fluid was found. Lumbar puncture on three different days showed 1, 2 and 2 cells respectively, yet at autopsy a chronic leptomeningitis was found in addition to visceral lesions associated with congenital syphilis. Nor does the severity of the cutaneous or visceral lesions bear any relation to the condition of the meninges, as illustrated by Case 24,998, aged three months, which in addition to a 4+ Wassermann reaction had anasarca, nephritis and syphilitic epiphysitis, yet only 4 cells were found in the cerebrospinal fluid.

A reduction with Benedict's solution was a uniform finding in the cases of congenital syphilis.

In 9 cases in which a quantitative test for dextrose was done it was within the normal in 8 cases and definitely reduced in only 1 case. These findings would lead one to believe that the quantitative estimation of dextrose shows that it is present in normal

amount in nearly every instance of congenital syphilis without meningitis in infancy. In 9 cases in which a quantitative estimation of the chlorids was made all were within the range of normal.

Of unusual interest is the following case of syphilitic meningitis proved at autopsy.

CASE X.—R. G. (23,945), a male infant, aged seven and a half months, was admitted to the Babies' Hospital on account of convulsions, weakness of voice, weakness of left arm, loss of weight and diminished excretion of urine. On lumbar puncture faintly turbid cerebrospinal fluid was withdrawn which showed 504 cells, 80 per cent of which were lymphocytes. The globulin test was strongly positive, the qualitative reaction for sugar was negative. The quantitative sugar determination showed 20 mg. per 100 cc of fluid and 700 mg. of chlorids. One week later lumbar puncture showed 1580 cells, mostly lymphocytes, a positive globulin reaction and a faintly positive reaction for sugar. The quantitative sugar showed 28 mg. and the chlorids 688. A third puncture showed a diminished number of cells and an increase in the quantity of sugar and 610 cells, with 37 mg. per 100 cc of fluid. The blood and cerebrospinal fluid showed a 4+ Wassermann reaction. The mother's blood Wassermann test was also strongly positive. In a precipitate of the cerebrospinal fluid no spirochetes were found. The eye grounds showed a low-grade retinitis. The infant was treated vigorously with neoarsphenamin intramuscularly and intravenously. He was also given arsphenaminized serum intrathecally. Death occurred after six weeks of observation.

Autopsy revealed cerebral hemorrhagic pachymeningitis and cerebral and spinal syphilitic leptomeningitis, in addition to the usual visceral lesions of congenital syphilis.

1. The intensity of the cutaneous manifestations of congenital syphilis is not a criterion of the findings in the cerebrospinal fluid.

2. Congenital syphilis may involve the central nervous system, as proved by a positive Wassermann reaction of the cerebrospinal fluid without causing a cellular reaction in the fluid.

3. A quantitative chemical analysis of the cerebrospinal fluid, for sugar and chlorid, in itself is not a helpful diagnostic item in the diagnosis of neurosyphilis; but taken in conjunction with the other findings it may add another positive point.

4. In syphilitic meningitis there is a reduction in the amount of sugar present in the cerebrospinal fluid, comparable to the reduction noted in other types of meningitis with high cell counts.

**Obscure Cases.** As evidence of the bizarre types of meningeal irritation not infrequently observed in infancy, particularly in early infancy, the following cases are presented. All were discharged from the Babies' Hospital with the note that they had given evidence of an undiagnosed condition of the meninges.

CASE XI.—H. M. (24,445), aged nineteen days, was admitted on account of convulsions, of which twelve had been noted during the twenty-four hours previous to admission. For a week he had not cried and had refused to nurse. The infant was somnolent. The umbilicus showed a slight discharge. The first lumbar puncture showed a clear fluid with 96 cells, mostly polymorphonuclears. The globulin reaction was sharply positive and the reaction for a reducing substance was positive. Five days later a second lumbar puncture showed slightly blood-tinged fluid with 264 white cells. The day following a cistern puncture showed a clear fluid with 96 cells. Subsequent counts were 176, 80, 28 and 83 respectively. Two quantitative sugar determinations showed a decreased amount, that is, 30 and 37 mg. per 100 cc of fluid. The culture of the blood and spinal fluid showed no growth. The Pirquet test, as would be expected, was negative. The infant was under observation thirty-five days and was discharged cured. He was examined at the age of eight months and was apparently normal. At that time the lumbar puncture revealed only 4 cells with a positive reaction for sugar and a negative globulin reaction. The blood and spinal fluid Wassermann tests were negative.

CASE XII.—M. S. (24,476), aged sixteen days, was a full-term infant, born after a difficult instrumental delivery. He was admitted to the Babies' Hospital with the statement that he had been normal until the tenth day of life when he became drowsy and refused to nurse. Convulsive movements were observed but no definite convulsions. His first lumbar puncture showed 19 cells, 60 per cent of which were lymphocytes. The test for a reducing substance was positive, as was the globulin test. Six days after admission 264 cells were present, the globulin test was positive and the quantitative sugar determination showed 39 mg. per 100 cc. Ten days after admission the cells had fallen to 87 and the globulin test was negative. Nineteen days after admission the cell count had fallen to 49 cells; the quantitative sugar remained practically the same, that is, 41 mg. per 100 cc. Moderate fever was present for five days. During the period of hospital observation symptoms pointing to mechanical obstruction to breathing were noted for several days. A profuse discharge of pus from the nose was followed by prompt relief of these symptoms. The infant was discharged cured after a month's period of hospital observation.

CASE XIII.—A. C. (24,874), aged twenty-five days, a full-term infant, normal delivery, with a birth weight of 6 pounds and 2 ounces, was admitted to the hospital on account of drowsiness for three days and refusal to nurse for three days. It was also stated that the infant had never cried vigorously, but that he seemed normal until three days prior to admission. The infant was

jaundiced, seemed drowsy and did not cry when disturbed. The first lumbar puncture showed 126 cells, 82 per cent of which were polymorphonuclears; the globulin test was positive as well as the test for sugar. Ten days after admission 70 cells were present. Sixteen days after admission the fluid showed 43 cells with 28 mg. of sugar per 100 cc of fluid with chlorids of 725. On the nineteenth day the fluid showed only 28 cells with a faint globulin reaction and 32 mg. of sugar and 688 of chlorids per 100 cc of fluid. Fever was present for twelve days. The infant was discharged on the thirtieth day cured of the condition for which he was admitted. At eight months of age he was apparently a normal infant.

CASE XIV.—D. C. (private patient, 819), aged four weeks. Normal labor; birth weight, $7\frac{3}{16}$ pounds; cried well at birth. Was normal for first three weeks of life. He then began to refuse to nurse and became drowsy. Three days after onset temperature rose to 103° F. and after a few days gradually subsided to normal. When four weeks of age he was in such poor condition that he was admitted to the hospital. He was transfused and a lumbar puncture was done. The cerebrospinal fluid was clear and showed 135 cells, 74 per cent of which were lymphocytes. A faint globulin reaction was present. The test for sugar was positive. The infant was discharged improved, and for two months after his acute illness his cry remained extremely feeble. At the age of six months he was somewhat backward physically but his mental development was normal.

Four cases are presented for diagnosis, all under one month of age. All had increased cell counts and positive globulin reactions. Three of the 4 showed diminished sugar in their spinal fluid. All were cured of the meningeal condition for which they were admitted to the hospital.

The following case differs greatly in symptomatology from the first three cases.

CASE XV.—P. P. (private patient), aged five weeks, was born after an easy labor, although low forceps were applied. The weight at birth was 7 pounds. The infant thrived during the first month of life, nursed well and gained normally in weight, but the mother was impressed with the type of cry, which to her never seemed vigorous. At the beginning of the fifth week the infant had a "cold." Fever was noted. He looked acutely ill, refused to nurse and showed weakness of the right arm. Examination revealed an apathetic infant with paralysis of the right arm and leg and paralysis of the right half of the abdominal wall, which showed distinct ballooning. Retention of urine was present. There was dilatation of the right pupil. The cry was extremely weak. The knee jerk was

diminished on the affected side; the day following it was absent and has remained so to date. A clonus was present on the affected side. The knee jerk was exaggerated on the left side. There was no bulging of the fontanel at any time. The routine laboratory tests, including blood, urine and Wassermann of blood and cerebrospinal fluid, were negative. Roentgen-ray showed the vertebral column apparently normal. Lumbar puncture showed 90 cells, 54 per cent of which were polymorphonuclears. The globulin test was strongly positive. Two days later the cells were reduced to 40, with a predominance of lymphocytes and a globulin test which was strongly positive. The infant is now four and a half months of age, well nourished and vigorous, but the arm and leg show spastic paralysis. The bladder symptoms and paralysis of the abdominal muscles disappeared a few days after they were first noted. The right pupil is still slightly larger than the left. Some improvement in muscle power has been noted in the upper arm and shoulder.

CASE XVI.—M. M. (24,532), admitted at the age of three days, is offered as a typical case of meningitis in the newborn caused by pyogenic organisms, in contrast with the cases just described. She had been a normal infant for the first two days of life. Convulsions began on the third day and a vaginal discharge and swelling of the right lower extremity was noted. A lumbar puncture showed 200 cells with yellow fluid, a negative sugar reaction and a strongly positive globulin test. Streptococcus hemolyticus was obtained from the umbilicus, the blood and the spinal fluid. Culture from the vaginal exudate showed Klebs-Loeffler bacilli. The infant died on the day of admission, and at autopsy a purulent leptomeningitis was observed in addition to diphtheria of the vulva.

**Bronchopneumonia.** The cerebrospinal fluid of 20 infants was examined in which the primary diagnosis was pneumonia. The majority of these cases were bronchopneumonia, many with complicating infections. The youngest case was twenty-eight days of age and the oldest was five years. Lumbar punctures were done in these cases because of symptoms which suggested the possibility of a central nervous lesion. Of the 20 cases, 9 died.

In every case the fluid obtained was clear and colorless, in 4 cases the test for globulin was positive, in 2 instances it was questionable and in 12 cases it was negative. The qualitative test for a reducing substance was positive in all the cases. In specimens of cerebrospinal fluid from several patients no cells could be found. The highest cell counts were 10, 12 and 10 and 11 respectively, and the average count for the 20 cases was 4 cells. The 4 cases with the highest cell counts died of pneumonia, the condition for which they were admitted to the hospital.

A quantitative sugar determination was done in 13 of the cases,

and in all it was within the range of normal, that is, between 45 and 85 mg. per 100 cc. The average for the 13 cases was 67 mg. per 100 cc, which might be taken as a normal for infants and young children. The lowest amount found was 47 mg., and the highest was 83 mg.

A qualitative determination of chlorids was done in 13 cases. These varied between 638 and 738 mg. per 100 cc, which is within the normal range, that is, 600 and 750.

Of interest is the fact that in these 20 cases, all of which had either one or more of such symptoms as irritability, rigidity of neck, vomiting, drowsiness, coma or convulsions, which led to the suspicion that the central nervous system might be invaded, yet not one had very marked increase in the number of cells nor had any of the group a marked change in the amount of dextrose. The only finding which could be termed pathological was a positive globulin reaction in 4 of 20 cases, which, in our opinion, was possibly due to the presence of a few red blood cells incident to the trauma produced by puncture. This is a commentary both as to the frequency of such symptoms in pneumococcic infections and the unreliability of the clinical signs of central nervous involvement in this type of infection.

**Disturbance of the Digestive System.** In this group of 10 cases are placed such conditions as dysentery, acute intestinal indigestion and intoxication. The youngest patient was four months of age and the oldest eight years. The average age was twenty-three and three-tenth months. In every instance the fluid was clear and colorless. In 8 cases in which a test for globulin was done it was positive in 3 cases and negative in 5 cases. The qualitative test for sugar was positive in all the cases. In 2 of the cases no cells could be found in the cerebrospinal fluid, and only 1 case in which 15 cells were found showed any appreciable cellular reaction.

A quantitative sugar determination was made one or more times in 8 of the cases. On the whole, this group showed a higher per cent of dextrose than the pneumonia group. The lowest showed 53 mg. per 100 cc and the highest 140. The average for nine estimations was 97 mg. per 100 cc as compared with 67 mg. for the first named group.

Several factors may have operated to cause this increase in sugar. Diarrheal cases admitted to an infant's hospital usually show a marked degree of dehydration as a result of frequent watery stools. In consequence, all of the body fluids, including the cerebrospinal fluid, would show varying degrees of concentration sufficient in many cases to increase the percentage of dextrose. In other cases treatment for dehydration with frequent injections of fluid under the skin, intraperitoneally, etc., might for a brief interval induce a saturation of the body tissues with fluid, and in conse-

quence a relative diminution of the solids, such as sugar, might occur. Many of these dehydrated infants are treated with hypodermoclyses of dextrose solution, varying in concentration from 3 to 6 per cent. The introduction into the body of 15 to 30 gm. of dextrose in the course of a few hours has been shown to raise the sugar value in the cerebrospinal fluid.

The chief interest from a clinical standpoint is the high percentage of sugar in some of the cases in this group, especially among those in which drowsiness or stupor occurred.

CASE XVII.—Of interest is E. M. (23,532), who, during two attacks of diarrhea at intervals of a year, presented symptoms which pointed to involvement of the central nervous system. The patient was admitted at the age of fourteen months because of vomiting and convulsions. Lumbar puncture revealed clear fluid with 15 cells, all of which were lymphocytes. The test for a reducing substance was positive. She was discharged cured, with the diagnosis of acute intestinal intoxication. She was readmitted at twenty-six months of age because of vomiting, drowsiness and convulsions. Lumbar puncture revealed only 4 cells, with a positive reaction for a reducing substance. The quantitative test for sugar showed 78 mg. per 100 cc and 700 mg. of chlorids. The blood Wassermann was negative. She was discharged cured, with the same diagnosis as on the previous admission.

This is a striking commentary on the tendency shown by certain children to manifest symptoms pointing to disturbance of the central nervous system in the presence of fever, whether due to infection or to chemical disturbance. In infancy the most common nervous symptoms are vomiting, irregular respiration, exaggeration of the reflexes, irritability, drowsiness, stupor and convulsions. In childhood the commoner symptoms are restlessness, as manifested by picking at the bed clothes, tossing about in bed, delirium, muscular tremor and coma. Some inherent defect in nervous tissue may possibly explain why certain children are prone to such symptoms in the presence of fever while others escape them altogether.

**Status Lymphaticus.** Three cases of status lymphaticus were demonstrated at autopsy in which lumbar punctures had been done during life. The ages were twenty-two months, sixteen months and five weeks respectively. In all 3 cases the cerebrospinal fluid was clear and colorless. The cell count showed 4, 6 and 25 cells respectively on the first lumbar puncture after admission to hospital. The reaction for a reducing substance was positive in all, and the globulin test was positive in 2. The quantitative sugar determination was well below the normal limits in 2 of the cases and normal in 1 case. The chlorids were normal in all 3 cases.

CASE XVIII.—P. F. (24,242) was admitted to the hospital at the age of five weeks because of irritability, rigidity of the neck and drowsiness. The diagnosis during life was sepsis. At the first lumbar puncture clear fluid was withdrawn which showed 25 cells, 60 per cent of which were polymorphonuclears. The test for a reducing substance was positive, and the test for globulin, which was only done on the fluid removed at the first puncture, was negative. Chemical analysis gave 33 mg. of sugar per 100 cc of fluid and 725 mg. of chlorids. A subsequent lumbar puncture showed a turbid fluid with 70 cells per cm., 71 mg. of sugar and 675 mg. of chlorids. A culture of the blood showed no growth. At autopsy a hyperplastic thymus weighing 30 gm. and an acute splenic tumor weighing 23 gm. were noted in addition to an hypertrophy of the pituitary. It semed likely that the infant's death had been hastened by the lymphatic state.

**Cerebral Hemorrhage Occurring at Birth.** The diagnosis of cerebral or cord hemorrhage can be made but rarely on lumbar puncture alone. Trauma produced by the needle frequently releases blood into the spinal canal. This is of such common occurrence in early infancy, even when performed with the greatest skill, that it invalidates the diagnosis of cerebral hemorrhage, if made on the presence of a few red blood cells or a large amount of blood in the cerebrospinal fluid obtained by lumbar puncture. If, however, bloody fluid is obtained at the first lumbar puncture performed in the first few days of life and successive punctures show a gradual diminution in the amount of blood, and eventually clear fluid is obtained, it may be held that cerebral hemorrhage has occurred.

If blood stained fluid is obtained by lumbar puncture in early infancy, and a yellow color does not disappear on standing or after centrifuging, it may be accepted as diagnostic of cerebral birth hemorrhage, because the xanthrochromia is the result of hemolysis.

The presence of bloody cerebrospinal fluid caused by cerebral hemorrhage at birth tends to disappear rapidly, and unless the hemorrhage has continued it will disappear entirely, usually by the end of the second week of life.

Such manifestations of cerebral hemorrhage as drowsiness, feeble respiration, feeble cry, refusal to nurse and a gray color of the skin, with or without convulsions or a bulging fontanel, are of greater significance to the clinician than the presence of a few red blood cells which may have resulted from trauma.

In the following group of cases lumbar puncture was done to exclude the possibility that an infection of the central nervous system might have been the cause of such symptoms as irritability, rigidity of the neck, exaggerated reflexes, convulsions, etc. Many of the infants were too old to consider the examination of cerebrospinal fluid as an aid in the diagnosis of cerebral hemorrhage due

to birth trauma. The diagnosis on discharge was made on the history of a difficult labor, the condition of the infant during the first few days of life plus the usual residual physical findings, supposedly denoting birth hemorrhage, which unfortunately are often purely speculative.

Of the 15 cases from two days to twenty-two months of age, with an average age of six months, only 3 showed xanthrochromic fluid. These were two days, five days and two months of age respectively. The average cell count for 15 cases was 5.4 cells per c.mm. One of the xanthrochromic fluids showed 14 cells per c.mm. and another 20 cells. None of the specimens of cerebrospinal fluid showed an increased cell count. The globulin reaction was positive in 4 of 14 cases, and the test for a reducing substance was positive in the 10 cases in which the reaction was done.

A quantitative test for sugar was done sixteen times in 11 patients; all were practically within normal limits. An infant, aged two days, with xanthrochromic fluid showed only 44 mg. of dextrose per 100 cc, which was confirmed on subsequent examination. A quantitative determination of chlorid was made on 11 patients, with sixteen examinations. All were within the range of normal.

**Conclusions.** 1. In cerebrospinal meningitis the sugar content of the cerebrospinal fluid is diminished in cases with moderately increased cell counts and absent in fluids with high cell counts, particularly purulent fluids. A gradual increase in the sugar was noted coincident with a decrease in the number of cells.

2. In a small group of cases of encephalitis the only uniform finding of diagnostic interest was a sugar content higher than in any other type of case.

3. In 3 cases of encephalitis, due to poisoning by lead, the test for globulin was positive, and in 2 of 3 cases there was pleocytosis.

4. In tuberculous meningitis the cellular reaction seems to bear no relationship to the number of tubercle bacilli in the cerebrospinal fluid.

5. A diminution of dextrose was noted in the cerebrospinal fluid of tuberculous meningitis, which might serve as a help in the early differential diagnosis between this disease and encephalitis.

6. There is little evidence of any diagnostic value in a chlorid determination in tuberculous meningitis, or in any other meningeal or extrameningeal conditions in infancy and early childhood.

7. In a small group of cases of pneumococcus meningitis the dextrose content of the cerebrospinal fluid was similar to the other purulent types of meningitis; that is, consistently low.

8. It was noted in a previous study of a group of cases of congenital syphilis, and again in this group that congenital syphilis may involve the central nervous system without showing an increase in the number of cells in the cerebrospinal fluid.

9. The quantitative estimation of dextrose in the cerebrospinal fluid of congenital syphilis showed it to be present in normal amounts in nearly every instance. In syphilitic meningitis there is a reduction in the amount of dextrose present in the cerebrospinal fluid comparable to the reduction noted in other types of meningitis with high cell counts.

10. In 13 cases of pneumonia the dextrose content of the cerebrospinal fluid was within the range accepted by us as normal. The highest cell counts in 20 cases were 10, 12, 10 and 11 respectively.

11. In a group of cases of disturbance of the digestive system an increased amount of dextrose was found. The results may be explained by the concentration of body fluids due to diarrhea and the introduction into the body of dextrose solution as a therapeutic measure.

12. If a blood stained fluid is obtained by lumbar puncture in the first few weeks of life, and the clear supernatant fluid is yellow, standing or after centrifuging, it may be accepted as evidence of cerebral hemorrhage. The presence of red blood cells in the cerebrospinal fluid obtained by lumbar puncture in the first few weeks of life is not diagnostic of cerebral hemorrhage, since the factor of blood introduced by trauma at the time of puncture cannot be excluded.

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## EARLY BED-SORES AS A DIAGNOSTIC SIGN OF CARBON MONOXID POISONING.

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Carbon monoxid poisoning is of rather frequent occurrence and any sign that will help in the diagnosis of obscure cases must be of value. It may result from inhalation of illuminating gas, coal-water gas, air vitiated by defective stoves, or the exhaust gases from the motors of automobile or motor boat leaking into a closed space. The danger is the greater because carbon monoxid of itself is a gas without special odor, color, or taste. There are cases on record of fatal poisoning from the gas conducted under ground from a distant location. The finding of an unconscious person, under circumstances leaving in doubt the cause of the coma, should awaken the suspicion of possible carbon monoxid poisoning.

Skin manifestations are not at all uncommon. Erythemas over cheeks and nose, localized edemas, vesicles, herpes, bullæ, red or bluish-red spots on the front of neck, trunk and thighs, purpuras and gangrene of extremities due to carbon monoxid poisoning have been noted. Very little can be found in the literature concerning

local necrosis and gangrene in areas exposed to pressure. It is the belief of the writer that these lesions are fairly common and are either overlooked, thought to be traumatic, or considered to be of no clinical significance.

The resulting carbon monoxid hemoglobin, which arises from the firm union of carbon monoxid with the hemoglobin of the red blood cell, is the primary cause of the clinical and pathological state which develops. This combination does not destroy the hemoglobin but prevents it from taking up oxygen, since the affinity of hemoglobin for carbon monoxid is three hundred times as great as that for oxygen. Straight tissue asphyxia arises because of the lack of tissue respiration. The formation of CO–Hb is evidenced by the cherry-red appearance of the blood during the early stages of asphyxia. Harbitz has shown that differences in susceptibility occur: Men, because of their need of more oxygen; those suffering from gastrointestinal, heart, lung, and exhaustive states are more susceptible and therefore succumb the more readily.

The early coma is due to severe damage to the ganglion cells of the cerebral cortex. If the patient survives the deep coma, a period of stupor followed by retrograde amnesia for events from the first to the fourth day of poisoning ensues. Therefore, the inability of many individuals to account for the cause or duration of their unconscious state. During the state of complete unconsciousness, the patient usually lies on his back, and the areas of skin that are in almost direct contact with the underlying bony structures—such as the prominence of the spine of the scapula near the vertebral border, sacrum, and heals—are markedly pressed upon. It is hardly likely that he would lie for any considerable period of time in the lateral position, in which event one would expect to find the early bed-sores over the elbow, superior spine of the ilium, great trochanter and external malleolus of one side. It is to be expected, that the less resilient the support on which the patient lies, the longer and deeper the coma, the longer a fixed position is maintained, the earlier and surer will these lesions appear. The mental dullness which frequently persists may be a factor in the failure of the patient to call attention to the lesion.

In these squeezed areas, the pressure causes constriction of the bloodvessels with possible secondary thrombosis. Anemic areas result, soon to be followed by atonic hyperemia. As a result of stasis and the diffusion of blood pigment, the area assumes a livid red color, which soon becomes discolored, moist, soft and gangrenous. Ulceration occurs. Healing is apt to be very slow and the areas may become secondarily infected with organisms from the skin or rectum. As with other types of ulceration, secondary bacteriemia and pyemia are possibilities.

The absence of tissue respiration and the continued pressure over certain vulnerable areas explain the early formation, within a few

days, of the bed-sores on the scapular, sacral and heel areas. Other factors may play contributory, though minor roles. (1) Heart weakness as evidenced by small pulse, low blood pressure and circulatory disturbances allows of peripheral stasis which in turn favors bed-sore formation. (2) Weak respiratory movements aid in decreasing circulatory movements and the rate of elimination of carbon monoxid, thus continuing the condition of tissue asphyxia which is so prominent a factor in the causation of this lesion.

**Case Reports.** CASE I.—Michael K. aged fifty years, was brought into the Greenpoint Hospital unconscious January 4, 1925. There was a questionable history of his having been found in a room in which there was an open gas jet. A venesection was done, removing 12 ounces of cherry-red blood. Slight rigidity of the neck, bilateral Kernig, slight left facial weakness, normal pupils, and spastic extremities were revealed on examination. A purpuric area was seen over the vertebral border of each scapula. A similar spot 3 inches in diameter was over the sacrum and there were purpuric areas the size of a half dollar over each heel. These were at first assumed to be bruises. The patient gradually recovered consciousness but his face remained expressionless and he responded sluggishly to questions. He had no recollection of what occurred and could throw no light on either the cause of his coma or the peculiar skin lesions. The Wassermann test of the blood and the blood chemistry were both negative. A spinal tap yielded clear fluid under slightly increased pressure containing 15 red cells and 5 polymorphonuclear leukocytes to the cubic millimeter, negative colloidal gold. The blood count 14,600 white blood cells, 80 per cent polymorphonuclears; 4,192,000 red blood cells. The temperature ranged between 100° and 102° F. for two weeks and gradually became normal. The pulse varied from 90 to 110; the systolic blood pressure was 110. The respiration ranged from 20 to 30. Within forty-eight hours after admission the purpuric spots on the heels and sacrum became definitely necrotic and gradually broke down. At the present writing almost two months later these bed-sores are not yet completely healed, and the patient presents a marked Parkinsonism. In this case because of the indefinite history, the finding of the red blood cells in the spinal fluid, fever, leukocytosis, initial coma and later evidences of meningeal irritation, it was assumed that the patient had sustained a basal meningeal hemorrhage. The early bed-sores were misinterpreted until the observation of identical lesions in the following case enabled us to make the correct diagnosis in retrospect.

CASE II.—John M., aged forty years, was found in bed unconscious. There was a heavy odor of gas in the room. After the use of the pulmotor he was brought to the Greenpoint Hospital

January 26, 1925. He could not be aroused. The pulse was rapid and full; blood pressure 80 systolic, 40 diastolic. Knee-jerks present, no Kernig or Babinski. Respiration 25, temperature 99° F. Less than forty-eight hours after admission the patient was found to have erythematous areas over both scapular regions and sacrum, with purpuric areas and bleb formations over both heels. There was marked cyanosis over the entire body. The day after admission he was semiconscious, face mask-like and his temperature, pulse and respiration gradually rising. Dullness, bronchial breathing and subcrepitant rales were found in right axilla and left posterior chest. Spinal tap yielded clear fluid under slightly increased pressure, 50 red blood cells, 5 lymphocytes and 5 polymorphonuclears to the cubic millimeter; normal Fehling reduction, no globulin increase and negative Wassermann. Blood count 14,400 white blood cells, 80 per cent polymorphonuclears, 4,500,000 red blood cells on second day. The patient died on the fifth day with a temperature of 102° F., pulse rate 120, and respirations 40 before exitus. It was the coincidence of the early bed-sore formation in two patients both in the ward at the same time, one a suspected and the other a definite case of gas poisoning, that called the attention of the writer to this phenomenon and the possibility of it being used as a diagnostic aid.

CASE III.—The writer is informed of a definite case of carbon monoxid poisoning in another hospital in an adult male, who on arousing from coma complaining of sores upon his back which he did not remember having had before the accident.

**Conclusion.** Carbon monoxid poisoning is attended by a great decrease of tissue respiration. The severely poisoned individual lies on his back for a considerable time and the resulting pressure over the scapular, sacral, and heel areas together with the above factor of tissue asphyxia leads to early bed-sore formation.

The very early appearance of bed-sores in a previously comatous or still stuporous individual is almost pathognomonic of carbon monoxid poisoning, and is not found as early in other conditions.

This sign is therefore of great value from a clinical and medico-legal viewpoint.

The writer wishes to express his thanks for the coöperation of Drs. J. Kasnetz, S. A. Seley and J. Weinstein for their search of the literature and hospital records in connection with the preparation of this paper.

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## PRIMARY CARCINOMA OF THE LUNG.

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Primary carcinoma of the lung is considered a rare condition by many writers. We frequently find in the literature such statements as "carcinoma is by far the most frequent form of malignant tumor of the lungs and yet it is absolutely and relatively infrequent;" "cancer of the lung may be primary or secondary, the former is rare, the latter common;" "while primary tumors are rare, secondary growths are not uncommon. Carcinoma is the most common primary form;" "primary carcinoma of the lung is an uncommon disease." However, within a comparatively short time we find the belief growing that this condition is not so rare as commonly supposed. "Increased interest in primary carcinoma of the lung in recent years has furnished statistics which indicate that the condition is more frequent than is usually stated" is a recent comment on the subject. Norris and Landis write, "primary carcinoma of the lung is generally looked upon as of relatively rare occurrence. This belief is not well founded according to Sailer and Torrey." Ewing states that "primary malignant tumors of the lung form about one per cent of all cancers. Secondary growths due to carcinoma are ten times more common than primary growths. Primary growths occur more frequently in males than females in a ratio of 3 to 1, while metastatic growths are more common in females. The chief etiologic factor is tuberculosis. Of Wolf's 31 cases, 13 were associated with tuberculosis. Squamous-cell carcinoma developing in the wall of a tuberculous cavity is described by Schwalbe, Friedländer and Perrone. Wolf found tuberculous lesions throughout diffuse carcinoma or surrounding tumor masses. Oertel points out that the association may be accidental, at other times the two processes exist in symbiosis, while rarely tuberculosis appears to inhibit the carcinoma. Several cases in which there

was active miliary tuberculosis with carcinoma suggest that the malignant process may light up latent tuberculous foci. Rupture of anthracotic nodes into the bronchi is held by Wolf as responsible for some cases of bronchial carcinoma." Other etiologic factors may be chronic bronchitis, chronic fibroid pneumonia and trauma.

The admission of 3 patients with primary carcinoma of the lung to the same ward at Kings County Hospital between February 12, 1924 and June 1, 1924, a period of three and a half months, causes the writer to believe that this condition is more common than is usually believed. Two of the patients were on the writer's service and one, L. H., was on the service of Dr. B. F. Corwin, whose service alternates with the writer's and who has kindly consented to allow a report of the case.

**Case Reports.** CASE I.—H. K., aged forty-nine years, was admitted to the writer's medical service, Kings County Hospital, February 12, 1924 and died February 24, 1924. His chief complaints were a productive cough with mucopurulent but not blood tinged sputum, which began two months before admission to the hospital; pain, which gradually developed in the left side of the chest, on admission was almost constant and increased on coughing; dyspnea was marked. Cough and pain were severe enough to prevent sleep. The patient had lost 10 pounds during the past two months and had grown progressively weaker. Aphonia was noticed six weeks before admission to the hospital. His associated symptoms were occasional fever, no chills, no sweats, a chronic productive cough, marked dyspnea, no palpitation, no precordial pain. There was occasional swelling of the ankles for the past year, absent in the morning but present when on his feet for some time. He had a fair appetite, no nausea, no vomiting, bowels regular, not medicated. He was easily fatigued, had lost weight, and slept poorly from pain and cough.

*Family history* shows his mother died of apoplexy, aged fifty-seven years, and his father of typhoid fever at thirty-six years; one brother is alive and well; two sisters died in childhood, cause not known to the patient; no history of tuberculosis or malignancy. Previous personal history: During childhood the patient had very severe attacks of scarlet fever and diphtheria. He also had measles, mumps and whooping cough. The patient states that he was a sickly child. During adult life the only disease was a bilateral, lower lobe, lobar pneumonia two years before admission to Kings County Hospital. There was a negative history for gonorrhea and lues.

*Physical examination* revealed a moderate framed, poorly-nourished, pale adult complaining of cough, pain in chest and shortness of breath. Head, eyes, nose and ears were negative. There was no glandular enlargement in the neck. Chest examina-

tion showed a narrow, poorly-nourished chest with diminished expansion of both sides. There was marked distention of the superficial veins of the chest. Tactile fremitus was diminished throughout the left chest. There was impaired resonance over both upper and lower lobes posteriorly on the left side, and harsh breathing with numerous loud moist rales throughout the left chest with dry friction rub over left base. The voice sounds were diminished throughout the left side. The abdomen showed no localized areas of tenderness, no palpable masses and no herniæ. The inguinal glands were palpable and shotty.

Abscess or malignancy of the lung or mediastinum was suspected. Roentgen-ray examination showed a neoplasm in the left upper lobe and one in the left lower lobe. A bronchoscopy was performed by Dr. M. C. Myerson who confirmed the diagnosis of malignancy of the lung; his report follows: "Upon entering the left main bronchus with the bronchoscope a very penetrating foul odor was noticeable which was not present before. When the bronchoscope came to a point opposite the upper lobe branch bronchus a viscid milky fluid was encountered. This fluid after evacuation was clearly demonstrated to come from the upper lobe bronchus. A special upper lobe suction tube was easily passed. The bronchoscopic picture confirms the diagnosis. There is no main bronchus pathology but probably some upper lobe branch bronchus pathology which cannot be seen."

During the patient's stay in the hospital the cough was always troublesome. Following the bronchoscopy the patient stated that he expectorated an entirely different type of sputum, having a bad taste and foul odor but raised very much more easily. The reason for this was that the left upper bronchus leading to the tumor was plugged and aspiration through the bronchoscope opened the occluded bronchus making expectoration easier and cough less painful. Five days after bronchoscopy the patient expectorated considerable foul smelling bloody sputum during the afternoon, his pulse became weak and rapid and he showed signs of collapse. At five o'clock the following morning he raised a large quantity of bright red blood and died of hemorrhage. The patient had a fever the first four days in the hospital, the highest point being 102.4° F.; the respirations rose as high as 34 per minute, averaging 26. The laboratory reports gave a normal urine; sputum negative for tubercle bacillus; blood Wassermann negative; blood chemistry normal. Microscopic examination of pus from the bronchus showed an admixture of fibrin, red blood cells and inflammatory cells. No malignant cells were observed.

The findings at autopsy were as follows; only those of positive interest being recorded here:

*Anatomic Findings.* Necrotic mass in upper lobe of left lung;

chronic pleuritis; petechial hemorrhages of right lung; pericardial effusion; left pleural effusion; perihepatitis; fatty cirrhosis; chronic interstitial splenitis; accessory spleen.

*Section.* On median incision and removal of the sternum there was found to be present a very small amount of subcutaneous fat. The peritoneal and right pleural cavities are free from fluid. The pericardium is distended and contains about 400 cc of straw-colored fluid. The left pleural cavity is obliterated except for the portion over the lower lobe posteriorly where there is a cavity containing about 600 cc of reddish-brown, foul-smelling fluid.

*Right Lung.* The right pleura is smooth and glistening, and a few petechial hemorrhages are found on its surface. The lung is moderately hypertrophied, pale and somewhat anthracotic. The lung floats in water, is well aërated and on section appears normal. The pulmonary arteries are empty.

*Left Lung.* The pleura over the entire lung is thickened. The upper lobe is nearly entirely replaced by a large, broken-down mass surrounded by indurated lung tissue. This tissue is not definitely encapsulated. The lower lung is infiltrated and edematous. The lung sinks in water.

*Trachea.* The trachea contains a bloody fluid throughout, and there is a large blood clot lodged in its upper portion, nearly occluding the lumen.

*Esophagus.* Contains bloody fluid throughout.

*Peribronchial Glands.* The peribronchial glands are not enlarged or calcified, but are the seat of anthracosis.

*Heart.* The heart weighs 400 gm. "Milk spots" are present on its posterior surface and there is some increase in the epicardial fat. The myocardium is pale but otherwise shows no lesion. The valves show no pathology.

*Aorta.* The aorta is normal throughout except for a few yellowish plaques in the descending portion.

*Cause of Death.* Pulmonary hemorrhage.

HISTOLOGIC DATA: *Heart.* Cloudy swelling; hydropic degeneration.

*Lungs.* Alveolar-cell carcinoma; pulmonary abscess; chronic pleuritis.

*Peribronchial Lymph Node.* Subacute and chronic hyperplastic lymphadenitis; no evidence of tumor metastases.

*Spleen.* Edema. *Liver.* Cloudy swelling; chronic perihepatitis.

*Adrenals.* Normal.

*Kidneys.* Focal areas of fibroblastic change, but on the whole the kidneys are practically normal. *Pancreas.* Normal. *Aorta.* Atheromatous.

Dr. Hala, pathologist at the Kings County Hospital, has given the following detailed report of the specimen of the left lung:

*Gross Description of the Lung.* The pleura over the entire lung is thickened. The bronchus is found filled with blood. There is no gross evidence of neoplasm affecting the bronchus. Upon transection of the lung, practically the entire upper lobe consists of a broken down, necrotic material surrounded by a peripheral wall of indurated lung tissue. The lower lobe shows scattering irregular areas, greyish pink in color, of varying size, from 2 mm. to 1.5 cm. in diameter. These areas suggest neoplasm.

*Microscopic Examination.* Sections show carcinoma in which the predominating type of tumor cell is cuboidal. In general the cells are in compact masses filling up the entire air sac, although occasionally they are found lining the alveolar wall. Numerous "giant" cells occur. Marked areas of necrosis are also outstanding features. Mitoses and amitoses are common. There is very little reticulum in the tumor proper. Focal abscesses are not uncommon. In a few areas, the tumor cells closely compacted assume more or less of a spindle shape.

This neoplasm is evidently derived from alveolar epithelium. It is rather difficult to classify it as either a diffuse carcinoma or multiple nodular carcinoma. The gross appearance of the lower lobe of this lung would seem to point to multiple nodular carcinoma, while the extensive involvement of the upper lobe favors diffuse carcinoma. It is possible, however, that the lesion was not really diffuse in the upper lobe, the predominating histopathology there being abscess formation. This case showed no metastases.

CASE II.—L. H., a Russian, aged fifty-one years, was admitted to the service of Dr. Corwin on March 1, 1924 and died March 31, 1924. The chief complaints on admission were pain in the right chest and back, productive cough and profuse night sweats. This condition had existed to the patient's knowledge for six weeks. The cough was productive of mucopurulent expectoration but no blood. The family history was negative. The patient's previous personal history was negative except for two broken ribs on left side thirteen years before the present illness. The physical examination showed a large-framed, poorly-nourished, white Russian male, clear mentally but unable to speak English. Scalp, eyes, ears and nose were negative. Mouth showed teeth and gums in poor condition. The cervical lymph glands on the right side were enlarged. There was also distention of the superficial veins of the right neck and shoulder. The chest was fairly well formed with prominent clavicles. There was a small nodular tumor over the left pectoral muscle. There were exaggerated breath sounds with areas of bronchovesicular breathing and impaired resonance with mucous rales throughout the lower right chest posteriorly. Heart sounds were regular, rapid and of fair quality. The heart was not enlarged. There were no murmurs present. Blood pressure, 110 systolic,

50 diastolic. The back, abdomen, genitals and extremities were negative. A provisional diagnosis was made of either chronic pulmonary tuberculosis, or mediastinal neoplasm extending into the right lung.

The subcutaneous tumor over the left pectoral was removed for diagnosis shortly after the patient's admission. The pathological report on the biopsy specimen follows: "The specimen consists of a section of a lymph node and a subcutaneous nodule. There is present a tumor composed of closely packed squamous epithelial cells showing both mitotic and amitotic changes. Diagnosis: Squamous celled carcinoma, metastatic."

It was noted that during examinations or during excitement the patient developed an urticarial reaction which was linear in type and appeared on the skin of the arms, chest and abdomen. Sixteen days after admission many subcutaneous nodules appeared over the body and extremities, and increased rapidly in number.

The report of a bronchoscopic examination by Dr. Myerson follows: "The trachea at about the fifth ring down to the middle of the right main bronchus shows a considerable dilatation on the right side posteriorly, with some right side displacement. The right main bronchus from ½ inch from the beginning as far as could be seen to the lower branch shows an irregular papillation of the mucous membrane."

Roentgen-ray of the chest showed a large irregular mass involving the middle and lower lobes of the right lung, pulling the trachea and heart to the right side. There was increased width and density of the mediastinal shadow. The left lung was clear. There was no fluid present. The laboratory reports showed a normal urine. Phenolsulphonephthalein test—37 per cent; 25 per cent; 12 per cent; total, three hours, 74 per cent. The sputum was negative for tubercle bacillus. The blood Wassermann was negative. Blood count and blood chemistry were normal. The temperature varied between 100° F. and 103° F. rectally. The pulse varied between 80 and 130 per minute. The respirations varied between 24 and 40 per minute.

The patient died one month after admission with signs of pulmonary edema.

The autopsy report follows:

*Anatomic Findings.* Primary carcinoma of the right bronchus; metastatic carcinoma throughout the body; pleural effusion (right); pericardial effusion; old healed scars; edema of the brain; chronic adhesive pleuritis, right; chronic passive congestion of the liver.

*Inspection.* It is the body of an emaciated, male, white, aged fifty-one years, weighing 150 pounds, and about 5 feet, 8 inches tall. Slight rigor mortis in present with postmortum lividity over the dependent parts. There is a small operative scar just above the sternal end of the clavicle on the right side about 2 inches long and

bears the marks of three sutures. There is an old healed scar about 1 inch long just below the midpart of the left clavicle. Over the entire body with the exception of the face, palms of the hands, soles of the feet, and the scalp, are seen subcutaneous tumors which vary in size from that of a pea to that of a walnut. On section these tumors are found to be adherent to the surrounding tissues and the deeper layers of the skin.

*Section.* On median incision, very little subcutaneous fat is found. The sternum is removed, the left pleural cavity and the peritoneal cavity are free from fluid. The right pleural cavity contains about 1800 cc of light brown fluid which solidifies on standing into a gelatin-like mass. The pericardium is distended with about 350 cc of light greenish-yellow fluid containing flakes of fibrin. The pleura, pericardium and peritoneum are smooth and glistening throughout.

*Head.* On reflecting the scalp and removing the calvarium, the brain is found to show some edema of the subarachnoid tissues. It is somewhat congested. On section no pathology is found.

*Neck.* The deep and superficial lymph nodes are enlarged and indurated. The peritracheal nodes are infiltrated.

*Trachea.* Appears normal throughout.

*Lungs.* The left lung well aërated and on section shows no pathology except a few small tumors at the base. The right lung lower lobe is adherent to the diaphragm posteriorly by a dense infiltrated band of tissue. The upper lobe is soft and crepitates, on section it appears normal. The middle and lower lobes are firm and feel indurated. On section these are found to be almost completely replaced by a neoplasm. The lumen of the bronchus just below the bifurcation of the trachea is nearly occluded by new growth which appears to arise from the epithelial lining.

*Mediastinum.* The neoplasm of the right lung extends into the tissues of the mediastinum, displacing the contents of that space to the left. The peribronchial and all of the lymph nodes of the mediastinum appear to be infiltrated with new growth. There is a large node about the size of a walnut between the trachea and the esophagus about 1 inch above the bifurcation. The trachea and the esophagus appear normal.

*Heart.* There is a small tumor nodule at the base anteriorly on the epicardium. Aside from this the organ appears normal.

*Aorta.* Appears normal throughout.

*Vena Cava.* At the bifurcation of the vena cava attached to its posterior wall and extending about 1 inch into the right common iliac and ½ inch into the left common iliac, there is a small mass of tissue resembling tumor tissue. It is freely movable and apparently has only one point of attachment.

*Stomach.* Moderately distended with mucus and undigested food. There is a peristaltic constriction at its middle. The mucosa appears normal. The rugæ are prominent.

*Intestines.* Duodenum and the jejunum appear normal. The mesentery is studded throughout with small pea-sized tumor nodules. At the midportion of the ileum are found two small tumor nodules at the mesenteric attachment and apparently invading the wall of the gut. The appendix is normal except for a small tumor nodule in the serosa. The colon and rectum are free from pathology.

*Liver.* Normal size; on section shows evidence of chronic passive congestion. The gall bladder is normally distended with bile stained fluid. At its fundus there is a small tumor nodule protruding to the inside.

*Spleen.* Mottled on section, otherwise normal.

*Pancreas.* Normal; peripancreatic tissues are invaded with small tumor nodules.

*Kidneys.* The kidneys show no gross pathology; there is a tumor mass at the upper pole of the right kidney which is pressing on the adrenal. There are a few small nodules in the perirenal tissue of the left kidney; the adrenals, ureters, bladder, prostate and testicle appear normal.

*Cause of Death.* Primary carcinoma of the right bronchus with metastases throughout the body.

HISTOLOGIC DATA: *Heart.* Adiposis epicardii; metastatic carnoma of epicardium; cloudy swelling of myocardium.

*Bronchus.* Primary squamous-cell carcinoma of bronchus.

*Lungs.* Squamous-cell carcinoma, the tumor showing in places marked degenerative changes.

*Peribronchial Node.* Metastatic carcinoma.

*Liver.* Chronic passive congestion; cloudy swelling.

*Gall Bladder.* Metastatic carcinoma.

*Spleen.* Chronic passive congestion; edema; atrophy of follicles.

*Pancreas.* Moderate adiposis; metastatic carcinoma of peripancreatic lymph nodes.

*Adrenals.* Metastatic carcinoma of periadrenal tissues. *Kidneys.* Metastatic carcinoma. *Appendix.* Metastatic carcinoma of mesoappendix. *Prostate.* Numerous corpora amylacia, otherwise normal.

*Intestine.* Metastatic carcinoma of ileum, situated in the subserous and serous coats. *Mesenteric Lymph Node.* Metastatic carcinoma.

*Skin.* Subcutaneous metastatic carcinoma. *Subcutaneous Node.* Metastatic carcinoma. *Brain.* Moderate congestion; edema.

Dr. Hala has given the following detailed report of the specimen of right lung:

*Gross Description.* The trachea appears normal throughout. The lower lobe of the right lung is adherent to the diaphragm. The upper lobe is soft and crepitant. The middle and lower lobes are firm and feel indurated. The lumen of the right bronchus

just below the bifurcation of the trachea is found almost occluded by a mass springing from the mucosa. Transection through the bronchus and bisecting the entire lung reveals the following pathologic picture: The upper lobe is moderately edematous but otherwise negative. The middle and lower lobes show large and small metastatic masses. The mass observed in the right bronchus extends through the wall inferiorly and invades the surrounding lung tissue. The mediastinal lymph nodes are enormously enlarged and apparently the seat of tumor metastases.

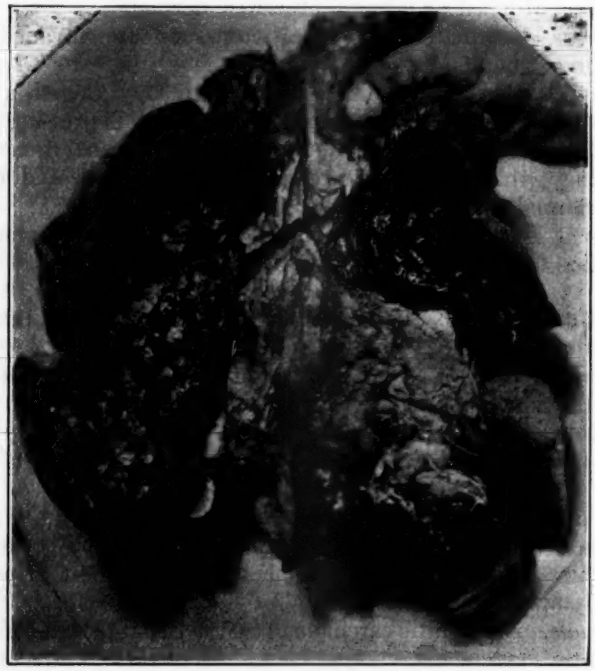

FIG. 1.—Photograph of gross specimen of lung of patient, L. H. Primary carcinoma of lung.

*Microscopic Examination.* Bronchus: For a considerable area the normal columnar ciliated epithelial lining is replaced by a heaped-up mass of squamous and large round epithelia, comprising a neoplastic process which is found invading the entire bronchial wall and growing out into the adjacent lung tissue. Lung: Several sections taken through the nodular masses observed grossly disclose a neoplastic process, similar structurally to that observed in the bronchial wall. The tumor shows no tendency to acanthomatous metaplasia, the type of tumor cell remaining the same wherever encountered.

Dr. Hala gave the following opinion: In this case we are dealing with a primary carcinoma of the lung, the original focus of which was the lining epithelium of the bronchus. It is a squamous-celled tumor. The outstanding features were the numerous metastases occurring as they did, into peribronchial and mediastinal nodes, into epicardium, gall bladder, peripancreatic nodes, periadrenal tissue, kidneys, mesoappendix, small intestines (ileum), mesenteric nodes and subcutaneous tissue in various parts of the body. In all these metastases, the tumor has faithfully preserved its original structure.

CASE III.—H. N., male, aged forty-nine years, was admitted to the writer's medical ward, Kings County Hospital, May 28, 1924, and remained until August 3, 1924, when he felt strong enough to return home. He remained at home until September 23, returning in poor condition and died September 30, 1924. His chief complaint on the first admission was weakness, loss of weight, and pain in the right chest. Patient stated that one year before admission, he had a cough with marked dyspnea which improved under treatment. The present illness began seven weeks before admission as a so-called bronchitis, with piercing pain in the right lower chest. This pain became worse on exertion. Dyspnea was marked. At another hospital where he was a patient until one week before admission he had a thoracentesis performed, with a dry tap, and a bronchoscopic examination by Dr. Myerson, with the finding that, the entire right main bronchus was occluded by a neoplasm extending to the bifurcation of the trachea. A specimen was removed which showed a field indicative of epithelial malignancy. He became gradually weaker at the other hospital. On admission we found a poorly-developed and emaciated male complaining of weakness, and pain in right side of the chest. The chest expansion was fair and limited on the right side. Tactile fremitus was diminished on the right side. There was flatness over the right chest with distant bronchial and bronchovesicular breathing over this side in several areas. There were diminished voice sounds over some areas, while in other places the voice sounds were increased. Occasional rales were heard. The heart was displaced slightly to the left.

There was slight, occasional cough and no dyspnea, the pain gradually diminished. During the latter part of June the patient was comfortable, had no complaints, seemed to be gaining weight, felt stronger and was allowed to sit up a few hours each day. On August 2, he was discharged at his own request as he felt stronger, had slight cough, no pain or dyspnea. He promised to return when he needed hospital care.

The sputum was negative for tubercle bacillus. Sputum examination for carcinoma cells showed an admixture of pus cells, fibrin

and elastic tissue fibers. Occasional squamous epithelia of normal appearance or undergoing degeneration were observed but no cells suggesting neoplasm were present.

The urine was normal; the phenolsulphonephthalein output was 22 per cent, 20 per cent, 10 per cent, total in three hours 52 per cent. The blood Wassermann was negative and blood chemistry normal. On May 31, 1924 the blood count was: Red cells 4,032,000; leukocytes 31,900; 81 per cent polymorphonuclears; 16 small mononuclears; 3 large mononuclears; 80 per cent hemoglobin. The temperature was normal notwithstanding the white cell count. Blood examination on June 6, 1924 showed red blood cells 4,480,000; white blood cells 13,700; 67 per cent polymorphonuclears; 18 small mononuclears; 9 large mononuclears; 2 transitionals; 4 eosinophiles; 75 per cent hemoglobin.

The patient returned to the hospital September 23, 1924, with the report that he had done well until two days before admission. At this time he had a very profuse foul-smelling expectoration, marked engorgement of the superficial veins of the chest, neck and head and marked edema of the right side of face. He complained of severe pain in the right chest and extreme dyspnea. The patient died one week after return to hospital.

Blood examination on September 24 showed: Red blood cells 3,840,000; white blood cells 8,700; 78 per cent polymorphonuclears; 13 small mononuclears; 7 large mononuclears, 2 transitionals; 60 per cent hemoglobin. The sputum showed no cells suggestive of malignancy. The autopsy findings follow:

*Anatomic Findings.* General anemia. Edema of the right upper extremity, right side of face and both feet. Chronic adhesive pleuritis, right side. Hydrothorax, left. Acute fibrinous pericarditis with effusion. Carcinoma of the right lung with necrosis and "abscess" cavity formation. Ulceration of right bronchus. Metastatic carcinoma of peribronchial and mediastinal nodes. Chronic parenchymatous nephritis. Atheroma of the aorta.

*Section.* On median section of the body there is a marked diminution of the subcutaneous fat which has an anemic, light lemon color. On exposing the thorax there is marked edema of the tissues of the anterior mediastinum. The right pleural cavity is entirely obliterated by adhesions. The left pleural cavity contains about 500 cc of serous fluid. The pericardial sac bulges and on incision is found to contain about 150 cc of straw-colored fluid, in which float flakes of fibrin.

*Lungs, Heart and Trachea.* The lungs, heart and trachea are removed *en masse.* The entire trachea and bronchi are opened up from behind; situated just below the bifurcation and affecting the right bronchus is a large opening which communicates with a large "abscess" cavity in the right lung, approximately the size of a fist. On transection of the right lung, the entire lung is studded with

irregular, wavy and somewhat circular areas of yellowish color which grossly are not unlike areas of caseation. The peribronchial and mediastinal glands, both anteriorly and posteriorly are matted together in one nodular mass. In some portions the mass is yellowish in color and suggests a caseous process. In other areas, it is slightly grayish in color, firmer and suggests new growth. The inner surface of the pericardial sac is granular and the seat of acute fibrinous inflammation. The epicardium throughout is markedly granular and also the seat of fibrinous inflammation.

*Cause of Death.* Carcinoma of right lung.

HISTOLOGIC DATA: *Left Lung.* Emphysema. Moderate congestion and edema. *Pericardium.* Acute exudative pericarditis.

*Bronchus and Esophagus.* Squamous-cell carcinoma of the bronchus infiltrating into peribronchial tissues and beginning to invade the esophageal wall. In one area the growth has extended to the mucosa of the esophagus. The mucosa of the bronchus is entirely necrotic.

*Right Lung.* Squamous-cell carcinoma. Multiple interstitial and bronchiectatic abscesses. Subacute and chronic pleuritis. Areas of necrosis.

*Mediastinal Lymph Nodes.* Metastatic squamous-cell carcinoma showing areas of keratinization. Areas of coagulation necrosis.

*Pancreas.* Moderate lipomatosis.

*Liver.* Moderate chronic passive congestion. Parenchymatous degeneration.

*Spleen.* Early chronic interstitial splenitis.

*Kidneys.* Edema; early chronic glomerulonephritis.

Dr. Hala has given the following detailed report of the specimen of right lung:

*Gross Description.* The lungs, heart, trachea and esophagus are removed *en masse.* Examination of the esophagus discloses no gross pathology. Upon opening the trachea and bronchi, a large opening is discovered in the right bronchus, just below the bifurcation of the trachea. This opening is found to communicate with what is evidently a large "abscess" cavity occupying the upper lobe of the right lung. This cavity is filled with necrotic, foul-smelling debris of distinctly yellowish color. Scattered throughout the rest of the lung are numerous, irregular, wavy or circular areas averaging $\frac{1}{2}$ cm. in diameter, yellowish in color and not unlike areas of caseation. The peribronchial and mediastinal nodes are enlarged, more or less matted together in one nodular mass. Upon section they are all yellowish in color and suggest caseous tuberculosis. Stains for acid-fast bacilli are negative. A tentative gross diagnosis of caseous tuberculosis, or possible necrosing carcinoma of the lung is made.

The left lung on section is normal.

*Microscopic Examination.* The mucosa of the bronchus is entirely necrotic. Beneath the necrotic debris, a neoplasm composed of masses of squamous epithelia, often arranged in stratified formation and simulating epidermis, is found invading the entire bronchial wall. Some normal submucous glands are still extant in the submucous coat. The new growth in one area has invaded the esophageal wall and infiltrated toward its lumen at one small, almost microscopic area, replacing the normal mucosa of the esophagus.

FIG. 2.—Photograph of gross specimen of lung of patient, H. N. Primary carcinoma of lung.

*Lung Sections.* In the lung, the neoplasm takes on a rather bizarre structure. In some areas the tumor cells line the air sacs with a single layer of rather large polyhedral cells, in other areas by palisaded layers of squamous cells. There is considerable fibrosis between these open air sacs. Such sections give the tumor a pseudo-adenomatous structure. In other sections the tumor retains its original form, that is, acanthoma. Marked areas of necrosis and

abscess formation are common, particularly bronchiectatic abscess. The same structure of acanthoma is retained in the metastases to the mediastinal nodes.

Comments by Dr. Hala upon this specimen follow: This case presents two possibilities. First, it may be a case of primary acanthoma of the esophagus with secondary involvement of the right bronchus and lung, or second, it may be a primary acanthoma of right bronchus with secondary involvement of the esophagus and lung. Against the first supposition is the fact that no gross evidence of tumor was observed in the esophageal lumen at the time of autopsy, nor did the patient ever display any signs or symptoms referable to this tract. Again it would be uncommon for a primary esophageal carcinoma to remain of microscopic size for any length of time. Favoring the second supposition is the fact that primary acanthoma of the bronchus has occurred: cases are cited by Wolf. Moreover, the gross pathology pointed to primary involvement of the bronchus, and the clinical symptoms and signs displayed by the patient were all referable to the bronchopulmonary tract. The curious feature of the case was the gross similarity to caseous tuberculosis.

Limiting cases to neoplasms arising either from bronchi or lung parenchyma, histogenetically three types of carcinoma occur:

1. Neoplasms originating from bronchial epithelium.
2. Neoplasms originating from bronchial mucous glands.
3. Neoplasms originating from alveolar epithelium.

Histologically, carcinomata arising from the bronchial epithelium are either squamous-cell or cylindrical-cell tumors. Among the squamous-cell types acanthomas have been described. Carcinoma arising from bronchial mucous glands is mainly adenomatous in structure, although atypical alveolar types also occur. Carcinoma arising from pulmonary alveoli structurally consists of cuboidal, cylindrical or flat cells, partially or completely filling up the air spaces.

Malignant growths may occur at any age. Up to the middle period of life they are almost invariably sarcoma; beyond middle life carcinoma is more frequent. In these cases we have one alveolar-cell carcinoma, and two arising from the bronchus.

Primary malignant growth may occur as a single large tumor, having its origin in the root of the lung and extending into the pulmonary tissue, or there may be a number of small nodules varying in size from a hazel nut to a small orange. Less commonly the lung may be studded with small nodules resembling miliary tubercles. This widespread distribution, sometimes referred to as carcinomatosis, is seen more frequently as a result of metastasis. The carcinomatous growths are of a white, grayish or grayish-yellow color and are of firm consistency. When they occur in the lung tissue, they are apt to be softer, and may break down and empty

into a bronchus, thus forming a cavity. Metastases to other parts of the body may take place and entirely mask the pulmonary lesion. Metastases to the brain are not an uncommon occurrence in tumor originating in the bronchi.

The symptoms and course of pulmonary carcinoma vary extremely, according to the type of the tumor and the conditions which have led to its development. A large number of cases have been regarded clinically as acute or chronic phthisis, and since tuberculosis is often present without bacilli in the sputum, a differential diagnosis may be impossible. An apparently sudden onset is often due to acute changes in a long-existent tumor. A long history of bronchitis with or without hemoptysis has preceded the discovery of bronchial tumors. The uncomplicated bronchial tumor usually gives physical signs of a progressive intrathoracic growth with cough, hemoptysis, pain, recurring pleural effusion, serous or bloody, dyspnea and cyanosis. About half the cases are of the pleuritic type. Extensive infiltration of the pleura with adhesions may prevent effusion. Fever must be referred to complications. Constitutional symptoms are the same as those of malignant growths in any portion of the body. The acuteness of the disease depends to a large extent upon the rapidity of development of the growth and upon the amount and location of the pressure it exerts. The onset is usually insidious with a gradual failure of health.

The cardinal symptoms of pulmonary growths are: (1) Pain; (2) dyspnea; (3) cough; (4) profuse expectoration; (5) fever from surrounding tissue involvement; (6) pleural effusion; (7) weakness. Not all of these symptoms are present in each case; our second case had no dyspnea notwithstanding extensive involvement and metastases. The presence of blood in the sputum or the occurrence of small hemoptyses is extremely common when the parenchyma is involved. Occasionally the expectorated blood is thick, dark in color, and closely resembles currant jelly; when present, it is highly suggestive of malignant disease. Symptoms referable to the blood vessels are not unusual, and, as a rule, the veins are more frequently affected than the arteries. As the result of pressure on the superior vena cava or one of its main tributaries, the veins over the upper part of the chest may become greatly dilated, varicose and tortuous. In addition the face, upper part of the thorax and arms may become cyanosed, swollen and edematous. The evidences of venous stasis may be limited to one side or may involve both sides. Cachexia is slight in uncomplicated cases. Terminal states are often marked by suppuration, pneumonia and gangrene. The duration of this condition has varied from ten days to four years. A fatal hemoptysis may be the only symptom. The immediate causes of death may be asthenia, hemorrhage, thrombosis, acute infections, pulmonary edema and asphyxia.

Roentgenography will not demonstrate primary malignant

growths in the lungs or bronchi early enough to be benefited by radical chest surgery. Bronchoscopy not only yields the information derived from a clear view of the growth itself, but also will permit the removal of a specimen for histologic examination. Myerson, who bronchoscoped each of these patients, writes in a personal communication: "From the viewpoint of early diagnosis, there is no one single procedure of as much value in carcinoma of the lung as bronchoscopy. The importance of this diagnostic procedure is increased by the fact that a majority of pulmonary malignancies originate in the bronchial tree. The exact proportion is difficult to state. When seen by the bronchoscopist, the average case has so extensive an involvement that surgery is out of the question. Radical removal is the only hope for these cases, early diagnosis is essential, and the bronchoscope is the most valuable agency available for early diagnosis."

The writer feels that he has been unusually fortunate in having under observation these somewhat unusual cases and has given the findings in detail. He wishes to take this opportunity to thank Dr. Hala, Dr. Myerson and Dr. Chapman, house physician, for the assistance they have rendered.

**Summary.** Primary carcinoma of the lung occurs more frequently than is usually believed. This condition does not cause marked symptoms early in the disease, nor do these symptoms differ greatly from those of pulmonary tuberculosis. The physical findings in these cases, however, are unilateral, thus differing from advanced pulmonary tuberculosis. It is necessary in order to discover this condition early that we should watch more closely: (1) Those patients who complain of persistent cough without demonstrable cause; (2) those who expectorate bloody sputum at intervals with no tubercle ever found in the sputum, and (3) those who complain of general weakness, loss of weight and do not react to the usual methods of treatment. Roentgenography does not aid in the early diagnosis of malignancy of the lungs or the bronchi. Bronchoscopic examination furnishes us with information of these conditions comparatively early and should be advised where indicated. The value of postmortem examinations, so frequently refused, is demonstrated in these cases.

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## BLOOD TRANSFUSION: ITS DANGERS AND LIMITED VALUE.

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Transfusion of blood is by no means a new procedure; its early history, going back many ages, has been described quite fully by Dutton.[1]

An epidemic of transfusion passed over the profession from 1863 to 1884, during which years many enthusiasts thought it a cure-all for practically everything. von Bergmann, in 1884, published an important work on this subject, and practically put an end to the epidemic. The French Government finally took a hand in the matter and forbade the procedure until the Faculty of Medicine should give its approval, but such approval was never given. (Ravdin.[2])

During the last few years what would seem to be another epidemic of blood transfusion has been passing over the country; but, thanks to the recognition of the differences in bloods and the possibilities of their typing, the death record has been much less pronounced, though still, if all unfortunate results were reported, it would doubtless be surprisingly large. Few physicians seem to know anything about the epidemic referred to above, and almost none seem to remember anything about the investigations made by Cullen, of the Johns Hopkins Hospital, referred to later. It would seem very wise, therefore, at this time to make an investigation of the present status of transfusion in an attempt to determine its real value, its dangers and its abuses. Recent literature should be reviewed and surgical opinion sought.

Peterson,[3] of New York, in discussing the value and limitations of blood transfusion, especially commends it in anemias following acute or chronic hemorrhages, and also in hemophilia, particularly perhaps in the newborn. He speaks favorably, but not enthusiastically, of its use in purpura and in what he calls hemorrhagic diseases in which he includes hemorrhage seen in icterus, sepsis, nephritis,

and so forth. He confesses disappointment in transfusion in septic conditions, in which, except for its transient stimulating and strengthening action, it seems to have little effect. Transfusion in diabetes, uremia and hyperthyroidism, he says, is practically valueless. He does not accept the theory of Crile as to its use. He says: "Many attempts on my part to influence the course of acute septicemia or bacteriemia by blood transfusion have proven futile." As to the method, he prefers the syringe-cannula or the syringe-stopcock-cannula as approaching more closely the vessel-to-vessel method.

In the discussion which followed the reading of this paper Lewisohn[3] expressed himself as heartily in accord with the writer as to the value and limitations of transfusion, but spoke highly of the citrate method of transfusion.

Heyd[3] considered transfusion as distinctly not indicated in cases of sepsis, and expressed regret that relatives frequently had exaggerated ideas of the value of transfusion in these cases. In regard to its use in acute sepsis he adds: "There is a very large financial and social aspect in the prevalent idea that blood transfusion should be used in all cases of acute sepsis. It only entails expense to the family, and does not in any appreciable way benefit the condition."

In closing the discussion, Peterson called attention to the dangers of transfusion and the sequelæ. He objected to its use in hopeless cases after other methods have failed, simply in the hope that it might be of benefit. "A procedure," he says, "which lends itself so readily to commercial exploitation is apt to come in for a certain amount of abuse."

In discussing pernicious anemia and transfusion Richard Cabot[4] speaks as follows: "I do not myself believe that the modern habit of treating it with transfusion prolongs life. It will improve the condition for a certain period of weeks. If we want to have a patient perform some particular act, or see some particular person coming from a distance, it is exactly the right thing to do. It will bring almost any patient up for a time. But if I had pernicious anemia I would not be transfused, would not take the bother."

Richard Lewisohn,[5] of New York, who has had very large experience in transfusion of blood, in commenting on the frequency with which chills follow transfusion, says that it does not seem to make much difference what technic is used, but that increasing experience with any technic tends to secure better results. He says that the most formidable chills are encountered in the treatment of leukemia and acute sepsis. "In both of these conditions," he adds, "transfusion is useless as a therapeutic measure, and sometimes causes grave danger to the patient. For this reason transfusion is strictly contraindicated in these conditions."

Copher,[6] of St. Louis, reports a study of 245 cases of blood transfusion. He has found that by no method of blood transfusion is

it possible to avoid the varying percentage of disagreeable reactions, these reactions being manifested by fever, malaise, nausea, vomiting, chilly sensations, actual chills, muscular pains, dyspnea, cyanosis, pruritus, urticaria and headache. The fever he has found varying from 2° to 10°. He refers to a number of cases of fatal hemolysis in which the usual tests for transfusion had been entirely negative. In his own work he had 2 cases of fatal hemolysis. In 1 of these cases the blood matching before and after transfusion was perfect, but typical symptoms developed with death on the eleventh day. In the other case there had been no blood testing, but although only a small amount of blood had been transfused death occurred with typical symptoms in fourteen hours. He reports 14 transfusions for acute hemorrhage, with 11 recoveries. In 11 transfusions for hemorrhage associated with supposed shock there were 4 recoveries. Three others recovered from the hemorrhage but died later. In 12 transfusions for shock there were 8 recoveries. He warns against transfusion in pernicious anemia, where the patient is in a particularly weakened condition, because the post-transfusion reactions have been fatal in certain cases. He admits that such transfusion is without curative or permanent value. In regard to transfusion in sepsis he reports very unfavorably, quoting from several other writers. In chronic infections with secondary anemia he reports benefit in several cases, but it is apparently because of the anemia rather than the sepsis.

In a paper on fatal anaphylaxis following blood transfusions, Carrington and Lee,[7] of Philadelphia, report a considerable number of deaths in their own practice and that of others, the deaths following usually in a few hours after transfusion, and in a number of cases at least the previous study of bloods had shown that they were entirely satisfactory. Different methods of transfusion had been used, but there seemed to have been little difference in the fatal results. Their own fatality occurred in a patient, aged seventy-five years, with pernicious anemia.

Lee,[8] in commenting on the fatality reported by Lee and Carrington, says that following that accident he discussed the matter with a number of surgeons and found 6 other cases with similar fatal results which had never been reported. "If," he says, "in their limited experience in such a short time they have been able to unearth so many cases, it is quite evident there are many more which should be reported in order that a true estimate of the danger of this procedure can be obtained, which has now become so common that it is referred to the nurses and interns in the hospitals." Several unreported deaths have occurred in Columbus.

Recio and Ficureas (cited by Lee) report 2 deaths out of 34 transfusions, both patients dying within three hours.

Landis[8] distinctly condemns transfusion in pernicious anemia,

He refers to Lichty's discussion on the same subject in the *Therapeutic Gazette* (July, 1923). Lichty thinks that such patients with transfusion will die sooner than those without. Each patient seems to have due him a certain number of remissions, and transfusion simply hurries him through the number to which he is entitled. He, therefore, would live longer without transfusions than with them, but in grave cases, with immediate danger, transfusion may cause the patient to rally and get over that immediate danger. He prefers, however, the old line treatment of hydrochloric acid and pepsin, with arsenic and hygienic measures.

Walter V. Brehm,[9] of Los Angeles, states that out of 2000 transfusions, the number of patients not being given, syphilis was transmitted to 2 patients suffering from pernicious anemia, the donors in these cases having a negative Wassermann test only four or five weeks previously. He refers to a third case, also of pernicious anemia, in which the son of the patient was the donor and transmitted a violent attack of syphilis, the chancre in his case being only five days old.

W. E. Lee,[10] at a joint meeting of the New York Surgical Society and the Philadelphia Academy of Medicine, said he had recently had a patient who, after very careful matching with a number of donors, was transfused by the citrate method with 500 cc of blood without any immediate reaction. One-half hour afterward, however, he developed a typical anaphylactic protein reaction with high fever, spasm of the unstriated muscles, asthmatic symptoms in the lungs with involuntary voiding of urine and several bowel movements. This subsided after one hour, but the man developed acute edema of the lungs and died eight hours after the transfusion.

Hermann[11] reports a case in which he transfused 200 cc of citrated blood in a patient with anemia after septic abortion. The transfusion was immediately followed by severe subjective and objective disturbances, and development of a hemorrhagic diathesis from which the patient died.

Bancroft[13] reports a case of anuria following transfusion in which life was finally saved by decapsulating the kidneys. In his paper he refers to 8 other cases of a similar character but with a fatal result in 6.

In cases of low hemoglobin content of the blood the important question sometimes arises as to the advisability of preoperative transfusion, but no satisfactory answer can be made unless the surgeon has some idea as to the real operative risk in such cases. A most exhaustive study of this subject appeared in a paper presented to the American Gynecological Society in 1913 by Cullen, of Baltimore.[12] His report embraces all the cases in the gynecological records of the Johns Hopkins Hospital, for the previous twenty-three years, in which the hemoglobin was 40 per cent or below. He

found 170 such cases, as follows: Bleeding uterine fibroids, 42 cases; hyperplasia of the endometrium, 23 cases; carcinoma of the cervix, 18 cases; while pelvic inflammations, retained placenta, tubal pregnancy and other conditions accounted for the rest. Several of the patients were moribund when brought in, dying within a few hours without operation. The hemoglobin percentages ran from 40 to 10. There were 49 cases with hemoglobin between 40 and 36 per cent; 30 between 35 and 31; 29 between 30 and 26; 30 between 25 and 20; 14 below 20. Minor operations, such as curettage under ether or the removal of a submucous myoma, seemed to be attended with little or no trouble; 17 patients were subjected to hysterectomy, with hemoglobin as low as 19 per cent in one instance. The results, he says, "clearly show that with a very low hemoglobin hysterectomy may be safely undertaken." Of all the patients operated upon only 13 succumbed. Study of these fatalities shows very conclusively that in none of them could death be attributed to the low hemoglobin, but to certain preceding conditions or complications of which the anemia was at the most only a small part. In his conclusion Cullen says it is clearly evident that as a rule patients with a relatively low hemoglobin stand pelvic or abdominal operations fairly well. He speaks of the importance of familiarity with the technic of transfusion, but it was evidently considered unnecessary in any of the cases which he reports.

In my own work I have never hesitated for a moment in regard to operation unless the hemoglobin was extremely low. Particularly have I been free from worry since the appearance of the article by Cullen. Three cases stand out very distinctly in my experience. In one of them the patient, a middle-aged woman, had been bleeding from the bowel for several years, was emaciated, anemic and very feeble. She had been operated upon in one of our local hospitals two or three times, but on each occasion after getting the abdomen open the operator had thrown up his hands and closed the incision. She was kept in Grant Hospital for five weeks, being kept absolutely in bed, and every effort made to improve her blood. We would get her hemoglobin up to 22 per cent, and then there would be a sudden hemorrhage and it would drop down again. After doing this several times I finally decided to operate when it again reached 22. At the operation I removed a snarl of small bowel, making the usual anastomosis. Examination of this snarl showed that there had been intestinal obstruction, but Nature had overcome it by ulceration between adherent loops of bowel above and below the obstruction. The ulcer persisted, however, and it was its persistent bleeding that caused her anemia. She made an excellent recovery, and got fat and hearty. In the second case the patient's hemoglobin was 19 per cent, according to Dr. Coons' report, but he afterward told me he had shaded it a little in the patient's favor, as it was really lower than that. She was

having persistent bleeding from a large uterine fibroid. Her general condition, however, seemed to be good, heart's action good and I made a rapid panhysterectomy from which she made an uninterrupted and rapid recovery. In the third case, very similar to the second, I had thought of using radium or roentgen ray to control the bleeding, but after she was brought to the city, where I saw her for the first time, I was told by two radiation specialists that it would take probably two weeks for the radiation to be of much benefit. It seemed to me that with the persistent loss of blood it would be better to operate than to delay. Her hemoglobin was 12 per cent the day she came in; the next morning she had a pretty sharp hemorrhage, and no one knows what it was at the hour of the operation. Her husband's blood was typed and found suitable for transfusion, and he was kept just outside ready for transfusion if necessary. A panhysterectomy was rapidly made; she went through it as though her hemoglobin had been normal, made a rapid recovery and has been well every since.

Some months ago I sent a questionnaire to nearly two score of the leading surgeons of the country, and received replies from over two-thirds. Two or three of the surgeons addressed, after acknowledging receipt of the communication, had replies furnished by young assistants who were doing the transfusion. In those cases the replies, while refreshing for their enthusiasm, were in marked contrast to the replies which were furnished personally by the surgeons. The questionnaire asked as to transfusion in acute sepsis, chronic sepsis, burns, different degrees of secondary anemia, primary anemia and other conditions.

Among those who pronounced it of no value in acute sepsis were Davis (of Birmingham), Horseley, McClure, Erdman, Cabot, Seelig, MacLaren, Deaver, Bevan, Gillette, Ill, Coffey, DaCosta and Finney. DaCosta, Finney and Cabot not only regarded it as useless but even dangerous; Ochsner and Mayo as of doubtful value.

In chronic sepsis it was looked upon as valueless, or practically so, by Finney, Ill, Ochsner, Seelig, MacLaren, Deaver and Bevan. Where sepsis is attended with pronounced anemia, several of the surgeons thought it might be of some value, namely, Davis, Horseley, McClure, Erdmann, Cabot, DaCosta and Mayo.

Practically none of the surgeons used it in burns. Finney pronounced it dangerous. Erdmann and Deaver would use it only when there is anemia. Ochsner, Seelig, Bevan and most of the others had never used it.

Nearly all of the surgeons agree that transfusion is unnecessary in any of the milder forms of secondary anemia. It can be used advantageously in the more serious forms provided the cause is not some hopeless disease and the transfusion is made in anticipation of an operation. It is looked upon as especially valuable in cases of acute anemia, the result of hemorrhage. Seelig calls

attention to the danger of a serious reaction in pronounced types of anemia when the patient is on the verge and reaction may prove fatal.

In pernicious anemia practically all of them agree that it is of no permanent value, though Ochsner and Percy claim to have had some excellent results in cases in which, in addition to the transfusion, splenectomy was performed. Several suggest the possibility of error in diagnosis in cases of apparent cure.

A few of the surgeons recommend it in certain conditions of shock, though Seelig states that he is "not keen about it."

Nearly all the writers prefer the direct whole blood transfusion, though at the Mayo Clinic they use the citrate, and Frazier, of Philadelphia, is strongly in favor of it.

A few items from the correspondence might be of interest: Thus Hoover, of Cleveland, warns against the danger of more than one transfusion in cases of septicemia, and thinks the first should be undertaken with great caution. He mentions three fatalities due to transfusion in cases of sepsis. He would not employ transfusion at all except in cases where the sepsis was connected with pronounced anemia, and thinks that the improvement, whatever it is, is due to improvement in the anemia and not to increased resistance of the patient.

From the Mayo Clinic the statement is made: "Wholesale transfusion should be condemned. The circumstances connected with every case should be the determining factors in the decision."

Pfaff, of Indianapolis, reports that he has had a few cases which went wrong seemingly from embolism. One patient developed a fatal pneumonia. Three have died rather suddenly following transfusion.

Coffey commenced transfusion in 1908, and thought for sometime that he was saving a lot of lives, but later experience taught him that most of these cases get well without transfusion, and he now transfuses only in cases of very low hemoglobin, and he adds that even in such cases the value is probably overestimated. He now uses transfusion a few times a year. His final paragraph reads: "It is a therapeutic measure which is probably being overworked to such an extent that the question might be raised as to whether, taken as a whole, the good it accomplishes greatly outweighs the bad."

Howard Kelly feels that transfusions are being overdone. "The temptation must be great, indeed, in many cases where the patient is ill and the doctor is anxious to do something dramatic to impress the family, and especially as the technic is comparatively simple."

Robert Abbe thinks the novelty and improved technic have excited many young men to rush into the field, and he fears that enthusiasm has run away with judgment in many cases.

MacLaren, in writing of pernicious anemia, says that some

years ago he was very enthusiastic about transfusion, but after following a large number of these cases in which transfusion was performed there seemed to be no doubt that it did these patients more harm than good, and many of the cases died earlier than they would have without transfusion.

Harvey Cushing says that his rule is to refrain from transfusion unless it is urgently called for as a life-saving measure for acute loss of blood. He adds that transfusion is used far more often than necessary and many recoveries are ascribed to transfusion which would have taken place, in some instances perhaps more rapidly, without it.

Bevan is quite pronounced in his views. He writes: "When I have seen a clinic in which dozens or scores of blood transfusions were made I felt that they were, with the exception of a very small percentage of cases, of no value, and employed without any sound indication." He cannot see any indication for it in acute or chronic sepsis, or in burns, but believes it has a definite indication in severe hemorrhage in which the hemoglobin has gone down sharply to less than 35 per cent; but even in these cases, he adds, it does not of course compare in any way with the surgical control of the bleeding if this is a possibility. His final paragraph reads: "In conclusion I would say this: Show me a clinic in which a large number of transfusions are being done, and I will show you a clinic in which a large number of unnecessary transfusions are made."

R. G. Hoskins, professor of physiology in the Ohio State University Medical Department, when asked if he knew of anything in the transfusion of blood which could physiologically antagonize infection, promptly replied that he did not. There can be no doubt that any benefit which may arise from transfusion in septic cases is due purely to the improvement in the anemia.

**Conclusions.** As a result of a study of the replies to the questionnaire and of the articles which have appeared during the last few years, the following conclusions have been reached:

1. Transfusion is a procedure by no means free of dangers, some of which are absolutely unavoidable.
2. It is of no value in acute sepsis, but its use in that condition is particularly dangerous.
3. In chronic sepsis its value is only in improving the anemia when that has reached a more or less dangerous point.
4. It is of no use in burns except in chronic stages when the main condition is that of anemia.
5. It is of no ultimate value in pernicious anemia, but its use is attended with more or less hazard, so that it is questionable if the end results are of any real benefit.
6. Its chief value is in conditions of profound shock or acute anemia from hemorrhage, as in postpartum hemorrhage, ruptured

ectopic pregnancy and so forth. Particularly is it of value when given immediately preceding or following some operative procedure in which acute hemorrhage forms an important factor.

7. It seems to have little or no value in shock unless that shock is the result of acute hemorrhage.

8. Its very great value in hemorrhages seen occasionally in newborn infants has apparently been conclusively established. It seems to be in such conditions unnecessary to type the mother's blood, which can be taken at once and the injection of a small amount into the vein of the infant, or preferably perhaps into the superior longitudinal sinus, may prove a life-saving procedure.

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# REVIEWS.

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INFECTIONS OF THE HAND. By ALLEN B. KANAVEL, M.D. Fifth edition. Pp. 499; 196 illustrations. Philadelphia: Lea & Febiger, 1925.

THE mere fact that this book has now entered the fifth edition is evidence enough of its true worth. It is, to the mind of the reviewer, the best book on the subject available to the profession. It is a well-recognized fact that infections of the hand are the worst treated surgical conditions with which we have to deal. This deplorable state of affairs is probably due to the fact that the medical profession at large does not understand the anatomy of the hand. The author has done extensive work in this most important branch of the subject, and if the reader avails himself of the information contained in these valuable pages he will obtain infinitely better results in his hand infections.

The book is replete with numerous illustrations that clarify the text to the nth degree.

No one doing surgery should be without this work.

E. E.

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A MANUAL OF PHYSICAL DIAGNOSIS. By AUSTIN FLINT, M.D., LL.D., late Professor of the Principles and Practice of Medicine and of Clinical Medicine in Bellevue Hospital Medical College; revised by HENRY C. THACHER, M.S., M.D., Attending Physician, Lincoln Hospital and Assistant Attending Physician, Roosevelt Hospital, New York. Ninth edition. Pp. 320; 26 illustrations. Philadelphia: Lea & Febiger, 1925. Price, $3.00.

THIS little work needs no introduction. It has long been a classic in the field of physical examination of the heart and lungs. Useful to the student because of its clearness and simplicity, it should be particularly valuable to the physician because of the detailed information on percussion and auscultation in diagnosis. In this the ninth edition additional emphasis has been placed on inspection and palpation and the sections on cardiac arrhythmias and incipient tuberculosis have been enlarged. R. K.

TUMORS OF THE SPINAL CORD. By CHARLES A. ELSBERG, M.D., Professor of Neurological Surgery, Columbia University. Pp. 421; 354 illustrations. New York City: Paul B. Hoeber, Inc., 1925.

FOR the neurologist or neurosurgeon this monograph presents particular interest. Based upon a careful study of the clinical records of 100 verified cases of spinal-cord tumor, a comprehensive idea of the development and progression of symptoms resulting from such lesions is afforded. The histories of 81 cases are given in detail with illustrations of the sensory findings and diagrams of the position of the lesion as disclosed at operation. Individual cases are discussed and important features stressed. The second half of the monograph is given over to consideration of the typical and atypical symptomatology of tumors at different cord levels with suggestions and explanations as to the reasons for the variations noted in the development of motor and sensory changes. The importance of the cerebrospinal fluid findings in diagnosis is stressed. The indications for and technic of operative treatment is outlined and well illustrated. The author has brought the subject of the diagnosis and treatment of spinal-cord tumors up to date, possibly in too great detail to appeal to one not interested in neurology or neurosurgery. But by those dealing with such cases this monograph should be welcomed, for it contains the results of close observation and the considered opinions of an experienced neurosurgeon.

F. G.

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PHYSIOLOGICAL PRINCIPLES IN TREATMENT. By W. LANDON BROWN, M.A., M.D. (CANTAB), F.R.C.P., Physician to St. Bartholomew's Hospital. Fifth edition. Pp. 511. New York: William Wood & Co., 1925. Price, $3.75.

THIS interesting book is the work of one who is both a practitioner of medicine and a teacher of physiology. Under headings, such as "irregular action of the heart," "glycosuria in diabetes," "the work of the liver," "the principles of organotherapy," he presents briefly and concisely our present knowledge of normal and deranged physiology and the application of these facts in rational treatment. The subject is presented in a very interesting and readable form, and is for the most part complete and correct in detail. American clinicians will miss any reference to the fractional method of gastric analysis and the phenoltetrachlorphthalein test of liver function. This book should be particularly valuable to the general practitioner who has not found it possible to keep abreast of the newer literature in physiology and physiological chemistry. Its usefulness and popularity are attested to by its five editions, two reprintings and translation into the Italian.

R. K.

DIET IN HEALTH AND DISEASE. By JULIUS FRIEDENWALD, M.D., Professor of Gastroenterology in the University of Maryland School of Medicine, and JOHN RUHRÄH, M.D., Professor of Diseases of Children in the University of Maryland. Sixth edtion. Pp. 987. Philadelphia: W. S. Saunders Company, 1925. Price, $8.00.

THE sixth edition of this excellent work represents a thorough revision with many additions and changes. The subject matter has been brought thoroughly up to date and certain chapters largely rewritten, notably those on diabetes, the use of insulin, vitamins and the deficiency diseases and food allergy. A number of new tables of food analyses have been included. The book is very valuable for reference, since it is encyclopedic in its information on dietetics. R. K.

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THE EMOTIONS, MORALITY AND THE BRAIN. By C. VON MONAKOW, Zurich; authorized translation by GERTRUDE BARNES and SMITH ELY JELLIFFE. Pp. 95. Washington and New York: Nervous and Mental Disease Publishing Company, 1925.

IN this monograph the author discusses the emotions and morality from purely physiologico-anatomical and physiologico-biological standpoints. He undertakes to demonstrate that the physiological basis of the emotions and morality is to be sought, "not only in the collective activities of the structures of the nervous system, or in the cortex, that is, in the so-called 'world of ideas,' but also in the internal secretions which work in and with these structures."

The book is divided into eight chapters, is very difficult reading, and presupposes a knowledge of anatomy, biology and heredity.

N. W.

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PATHOLOGY AND BACTERIOLOGY OF THE EYE. By E. TREACHER COLLINS, F.R.C.S., Consulting Surgeon to the Royal London Ophthalmic Hospital, and M. STEPHEN MAYOU, F.R.C.S., Surgeon to the Central London Ophthalmic Hospital. Second edition. Pp. 731, 4 colored plates and 306 illustrations. Philadelphia: P. Blakiston's Son & Co., 1925.

THE second edition of this well-known work contains 173 additional pages, and includes recent literature on various phases of ocular pathology. Thus, work on experimental embryology and genetics, such as the production and inheritance of developmental defects through lens antigen, is discussed.

A beginning has been made to correlate the findings of the slit-lamp with the histological picture.

The arrangement of material is like that in the first edition. Although this makes for interesting reading, various phases of a subject are so scattered throughout the pages that it is less serviceable as a reference book, especially in the absence of a complete cross-reference index. F. A.

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FEEDING, DIET AND THE GENERAL CARE OF CHILDREN. By ALBERT J. BELL, A.B., M.D., Assistant Professor of Pediatrics, Medical Department of the University of Cincinnati. Second edition. Pp. 290; 11 illustrations. Philadelphia: F. A. Davis Company, 1924.

A "POPULAR" book, which in two years has had one reprinting and now appears in revised edition, needs no reviewers' opinion. Suffice it to say that this compend of childrens' "do's and don't's," diets and weights, for mothers and nurses, is plainly and concisely written. To recommend its purchase to the new mother will save the pediatrician many useless and time-consuming queries.

C. L.

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A TREATISE ON MATERIA MEDICA AND THERAPEUTICS. By the late R. GHOSH. Tenth edition. Pp. 718. Calcutta: Hilton & Co., 1925. A TREATISE ON HYGIENE AND PUBLIC HEALTH. By B. N. GHOSH. Fifth edition. Pp. 586. Calcutta: Hilton & Co., 1924. MATERIA MEDICA. By B. N. GHOSH. Pp. 396. Calcutta: Hilton & Co., 1923.

THESE small books are deservedly popular in India and the tropics. Earlier editions of the first two have already been reviewed in these columns. The last named, on account of the differences of British and American pharmacopeias, will not be in great demand in this country. E. K.

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PSEUDO-APPENDICITIS. By THIERRY DE MARTEL, Surgeon to the Hospitals of Paris, and EDOUARD ANTOINE, Physician to the Hospitals of Paris. Translated from the French by JAMES A. EVANS, A.B., M.D. Pp. 211; 41 illustrations. Philadelphia: F. A. Davis Company, 1925.

THIS book answers the trident problem of the right lower abdominal quadrant: is it "a simple functional disorder of the proximal colon, a subacute or chronic appendicitis or a painful mechanical syndrome of the right ceco-colon?" The first fifty pages are devoted to clinical and roentgenological technique, and the rest of the book

to the clinical aspects, differential diagnosis and treatment, both medical and surgical, of the six types of "painful syndromes of the right ceco-colon." The intricate and painstaking detail of the work is a warning against the formula: "Dyspepsia plus pain over McBurney's point equals appendectomy." Lucid, conservative, based on the joint experience of physician and surgeon, it probably represents the golden mean in the modern philosophy of the right lower quadrant. C. L.

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CLINICAL MEDICINE FOR NURSES. By PAUL H. RINGER, M.D., Chief of Medical Service of the Asheville Mission Hospital, Asheville, N. C. Second edition. Pp. 306; 12 illustrations. Philadelphia: F. A. Davis Company, 1924.

IN this new edition the author has rewritten a considerable amount of material, and has introduced new subject matter on auricular fibrillation and Eggleston's method of digitalization. The author makes no claim to originality in the subject matter, but he has used considerable originality in his method of presenting it, with good effect. The material is authoritative, clear and concise. One wonders, however, just why he has not included all the diseases of the circulatory system together. Chapters III to IX are concerned with the circulatory system, as well as Chapters XXXI and XXXII. However, this is a small matter in view of the other good outstanding features of the book. He has definitely stressed the nursing care and correlated it very well with the pathology and symptomatology. S. G.

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FUNDAMENTALS OF HUMAN PHYSIOLOGY. By R. G. PEARCE, formerly Director of Medical Research Laboratory, Lakeside Hospital, Cleveland, Ohio, and J. J. R. MACLEOD, Professor in the University of Toronto, Toronto, Canada. Third edition. Pp. 349; 71 illustrations. St. Louis: The C. V. Mosby Company, 1924.

THIS is a short exposition of the various facts and theories included under physiology, as well as some histology and anatomy. It is of great benefit to beginners to have an elementary treatise written by men who have an extensive knowledge of the subject, and who select in the fulness of their judgment only the outstanding features. This is what made Huxley's elementary physiology of such lasting value to more than one generation of students. That the present book is found useful is evidenced by the demand for a third edition. W. A.

THE EFFECTS OF INANITION AND MALNUTRITION UPON GROWTH AND STRUCTURE. By C. M. JACKSON, Professor and Director of the Department of Anatomy, University of Minnesota. Pp. 616; 117 illustration. Philadelphia: P. Blakiston's Son & Co., 1925.

THIS is an authoritative work written from the standpoint of the gross and microscopic anatomist. It is a veritable storehouse of information on the subjects of inanition and malnutrition, not only in the vertebrates, but also in the invertebrates, including the protozoa, and in plants. It is a very timely volume inasmuch as it serves to fill a gap in our knowledge, by bringing together information which has been scattered through a diversified literature. The fact that the bibliography consists of 107 pages, with an average of 25 titles to a page, is an indication of the very substantial foundation on which the book is written. In addition, extensive researches have been carried out in the author's laboratory by himself and his staff. This gives a note of assurance to the author's analyses, and enhances the value of the work. In the part devoted to vertebrates there are 25 chapters. The first describes the effects on the body, as a whole, in total inanition; the second, in partial inanition. The remaining chapters describe the effects on the gross and microscopic structure of the separate organs. It will be of especial value as a book of reference, and will be consulted not only by anatomists and physiologists, but also by pathologists and physicians. W. A.

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DISEASES OF THE MALE ORGANS OF GENERATION. By KENNETH M. WALKER, F.R.C.S., M.B., B.C. Jacksonian Prizeman and Hunterian Professor, Royal College of Surgeons. First edition. Pp. 230; 78 illustrations and 1 colored plate. London: Henry Frowde, Hodder & Stoughton, Oxford Medical Publications, American Branch, 1923.

A SMALL book devoted to andrology and purposely omitting the voluminous details of the so-called venereal diseases. The chapters deal with prostatic hypertrophy and carcinoma, chronic prostatitis and vesiculitis, genital tuberculosis, injuries and diseases of testis, epididymis, spermatic cord, penis and scrotum, with short chapters on sterility and neuroses. The book is carefully written, contains the best of modern thought and teaching and is presented in a very readable style. Some parts are especially commendable and deserve wide publicity and reading, such as how to massage the prostate, the deciding factor in varicocele, the subject of genital tuberculosis and prostatic carcinoma. A. R.

# PROGRESS

OF

# MEDICAL SCIENCE

## MEDICINE

UNDER THE CHARGE OF

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**Distinctive Characteristics of Infections Produced by Treponema Pertenue in the Rabbit.**—A great deal of discussion has, in the past, taken place between those who maintain that yaws is a clinical entity and those observers who hold that it is an attenuated form of syphilis. This question of the unity or duality of the two diseases, write L. PEARCE and W. H. BROWN (*Jour. Exper. Med.*, 1925, **41**, 673) has been intensified by the fact that the morphological characteristics of Treponema pertenue and Treponema pallidum are similar and that infection of experimental animals with Treponema pertenue produced lesions closely resembling those of experimental syphilis. In order to discover if there was not some dissimilarity which had been overlooked, employing two strains of organisms of undoubted yaws, they injected a series of rabbits intratesticularly, using a technique similar to that in their syphilitic animals. The injections produced changes which differed in three essential respects from those of experimental Treponema pallidum infection. In the first place, and most characteristically, there was brought about an early granular periorchitis recognizable by palpation approximately three weeks after inoculation. This picture of multiple tiny nodules of the tunic without diffuse thickening of this structure has never been observed by the authors in experimental syphilis of the rabbit. Second, they find that there is no generalized manifestation of the disease elsewhere in the body, and last, a clinical lymphadenitis does not occur regularly. They note also that regression and healing of this granular periorchitis takes place in the majority of animals within three months after the original inoculation.

**Jaundice as an Expression of the Physiological Wastage of Corpuscles.**—It is frequently observed clinically that in the persistent obstructive jaundice of carcinoma of the head of the pancreas, the degree of the jaundice is most marked at the onset of the condition and gradually becomes less intense as the patient develops the cachexia of carcinoma. Likewise those who have worked with the van den Bergh test or the icterus index have learned to appreciate that marked bilirubinemia may be present with but slight if any icteric tint to the tissues. An explanation of these phenomena is present in a recent publication of PEYTON ROUS and D. R. DRURY (*Jour. Exper. Med.*, 1925, **41**, 601). They intubated the common duct of animals and made simultaneous daily quantitative estimations of the hemoglobin and the bilirubin content of the blood before and after induced hemorrhage. It was found that a very direct relationship exists between the two and that there are definite concurrent variations in hemoglobin percentage and bilirubinemia. The jaundice that develops after experimental obstruction of the common duct expresses the physiological wastage of corpuscles from day to day. After hemorrhage there is much less wastage; consequently there is less icterus. In anemic animals there is less hemoglobin and less jaundice. As the hemoglobin regeneration takes place, the degree of icterus increases to a concurrent degree. This close relationship between the intercurrent changes in bilirubinemia and hemoglobin shows that there is a distinct barrier to the distribution of bile pigment for the blood and this lies in the bloodvessel walls themselves. The authors state that "tissue icterus should be thought of as, ordinarily, the highly imperfect secondary expression of a condition which tends to be localized to the blood pool."

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**Notes on the "Thick-film" Method of Examination for Malarial Parasites.**—As a result of this study in one year of over 10,000 blood films for the presence or absence of malaria parasites, T. A. SINTON (*Indian Jour. Med. Res.*, 1925, **12**, 537) is convinced of the necessity of workers in this field acquainting themselves with the thick-film method of examination. He writes that while it has certain definite objections, these are more than overbalanced by the ease and rapidity with which the parasites are found by those familiar with the technique. In substantiation of his remarks as to the value of the method he quotes a large series of experiments which in round figures show that in hunting for Plasmodium vivax the thick film is six times as rapid as the thin film method and with Plasmodium falciparum approximately twenty times quicker than the older method.

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**The Relation of Sprue and Pernicious Anemia to Each Other and to the Monilia Psilosis.**—At first blush one would without hesitance say that sprue and pernicious anemia were diseases which present totally unlike clinical pictures and would rather scoff at the suggestion that the two diseases are one and the same, differing only slightly in their manifestations. Such apparently was the reaction of some keen clinicians, judging from the discussion at the end of a recent paper by E. J. WOOD (*South. Med. Jour.*, 1925, **18**, 153). However, the author presents his arguments clearly and concisely and backs them up by some experimental work which is not detailed in this article but evi-

dently reserved for a more complete report. He calls attention to the salient features of sprue, the characteristic tongue, the diarrhea, the frequent achylia gastrica, the anemia and the occasional occurrence of cord changes, symptoms all that are found in pernicious anemia. Both diseases have a tendency to run a course which is essentially chronic and which is subject to exacerbations more or less prolonged. Having presented the clinical similarity of the two conditions, the author then proceeds to discuss the etiology of the two conditions. He believes that Ashford's contention that sprue is caused by Monilia psilosis is well substantiated and assuming this to be true, he finds as further evidence of the unity of the two presumably different diseases, that Monilia psilosis is generally found in the mouth of the individual suffering from pernicious anemia. Further substantiation of this thesis is found in the experimental hemolytic type of anemia produced in animals by the injection of filtered extracts of the monilia. The chief objections to this theory of Wood as revealed in the discussion were largely objections of fact. The discussors of his paper stated that in their cases of sprue they rarely found achylia, that yeasts are not found in pernicious anemia, that the blood picture of sprue is usually of the secondary type, and that sprue is essentially a tropical disease whereas pernicious anemia has a widespread worldwide geographic distribution. The crux of the matter would seem to be in the question of the monilia causing sprue, which opinion is forcibly upheld by Ashford, or even more remotely causing pernicious anemia. Castellani holds that in sprue the monilia is merely a secondary invader and just as bacteria other than the tubercle bacilli are responsible for many of the symptoms in tuberculosis, so in sprue many of the clinical symptoms are produced by the secondarily invading yeast which is not, however, the primary cause of the disease. No matter what may be the ultimate outcome of this theory, its pronouncement by the author will undoubtedly lead to much study and eventually the etiology of the two disorders will be discovered.

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**Subacute Combined Degeneration of the Spinal Cord.**—A. F. HURST (*Lancet*, 1925, **208**, 397), at a recent meeting of the Neurological Section of the Royal Society of Medicine, discussed the relationship of pernicious anemia and posterolateral sclerosis of the cord, as observed by him in 21 cases of the latter disease. He demonstrated that the anemia which was present in this disease fulfilled all criteria for pernicious anemia, the characteristic blood picture, the glossitis, the achlorhydria all being present. It therefore seemed to the author that the two diseases are of identical pathogenesis, the disease manifesting itself in several ways according to the system involved, hemopoietic or spinal. He attributed both manifestations to the action of two different toxins, a hemolytic and a neurotoxic, which developed as a result of achylia. He argued that achylia is known to precede the development of pernicious anemia and posterolateral sclerosis. As a result of this achylia, hemolytic streptococci are admitted to the duodenum, to grow and to produce specific toxins. To substantiate this contention he showed that in a series of 42 cases of combined sclerosis and pernicious anemia from 77 per cent streptococci were isolated by duodenal drainage, whereas in 150 cases of other diseases

these organisms were found in only 21 per cent. The streptococci, moreover, were of the hemolytic type in 17 of the 19 cases of pernicious anemia and combined sclerosis in which they were examined and in the other 2 cases of combined sclerosis there was but slight anemia. That these streptococci gain entrance through the mouth is not an essential conception, but glossitis was present in 85 per cent of cases. In the discussion of this paper other observers are quoted as saying that in their series of cases achylia was not present in a goodly number of the patients. It would seem from this last statement that other types of anemia were confused with true Addisonian anemia by these observers because in this country at least hematologists are quite generally agreed this achylia is a *sine qua non* for the diagnosis of the blood disorder known as pernicious anemia.

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**Gastric Motor Activity in Patients with Peptic Ulcer.**—M. ORTMAYER (*Arch. Int. Med.*, 1925, **35**, 423) in her study of the motor activity of 29 patients with gastric ulcer lays stress upon one point about which there has always been more or less contention and which has never been satisfactorily answered, namely, the genesis of pain in gastric ulcer. She shows that the quite generally accepted theory of Carlson, that pain is the result of peristaltic contractions when the ulcer is in an "irritable state" does not hold good insofar as this can be proven by the method of recording peristaltic movement by means of an intragastric balloon. In 19 of the cases studied after the pain was relieved there was an increase in peristaltic movement following alkali in 10 of them, while 9 showed no change in peristaltic activity. These results would tend to show that pain and peristalsis are probably coincidental.

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**Experimental Morphin Poisoning.**—L. C. SCOTT, F. A. LORIA and J. C. TARDO (*Arch. Int. Med.*, 1925, **35**, 472) write that as there is but little known as to the manner of destruction, or at least the alteration of the alkaloid morphin within the body, they consider it worth while to investigate this problem as well as to determine if any disturbance in heart function resulted from the withdrawal of the drug in habituated dogs and, if so, to see if serum from these dogs when injected into normal dogs would produce similar changes as a result of some unknown substance circulating in the blood. The authors' first proposition, the destruction of the drug in the body, was shown by their experiments to be the result of some detoxifying action of the liver; the last premise was not proven. Incidental observations upon the action of morphin in long-continued dosage were of interest and may be briefly summarized: Immunity developed by increased dosage disappears very rapidly; whole blood does not protect an animal; morphin, as contrasted with quinin, is not abstracted from serum by the erythrocytes; morphin when injected into the portal circulation passes rapidly into the systemic circulation in some altered form.

# SURGERY

UNDER THE CHARGE OF

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**Splenic Anemia.**—HANSAHAN (*Arch. Surg.*, 1925, **10**, 639) states that it has been pointed out that there are four features of the examination that yield very suggestive information regarding a case of splenic anemia, namely, the duration of the symptoms, the blood examinations, the red blood-cell resistance and the urobilin excretion. The three most prominent phenomena following splenectomy in normal dogs, as observed by Pearce and his co-workers, were a secondary anemia, an increased resistance of the red blood cells to various physical, chemical and biologic agents and a lessened tendency to hemoglobinuria and jaundice, after the administration of hemolytic agents. The poor results following splenectomy in the acute and severe anemias, particularly in those that are pernicious in type, is probably explained by the fact that the operation does not remove the cause of the disease process. Cases with a white blood count of 5000 were considered as dividing-line cases between moderate and marked leukopenia. Cases with a marked leukopenia have a bad prognosis without splenectomy, and that this is modified by the operation is seen from the fact that 50 per cent of such patients are living. Cases having a moderate leukopenia have a good prognosis without splenectomy, while the prognosis with operation is no better than that observed in the cases with a marked leukopenia. The effect of the removal of a diseased spleen on the blood in anemia is dissimilar to the effect of removal of a healthy spleen on normal blood, as seen in experimental animals. There is an immediate and great increase in the white cell count, which gradually returns to normal in a month.

**Surgical Significance of Hepatic Function.**—WALTERS (*Minnesota Med.* 1925, **8**, 146) says that Counsellor, of the Mayo Foundation, studying sections of liver from jaundiced animals and specimens of liver removed at operation from patients with obstructive jaundice, believes that there may be a definite ratio between the number of abnormal hepatic cells and the amount of retention of the tetrachlorphthalein in the blood stream. It seems reasonable that tests of the glycogenic or sugar-storing function of the liver might serve also as an index of hepatic function. Strauss, in 1901, gave levulose by mouth to patients with hepatic disease, and found that levulose appeared in the urine of 90 per cent, because the diseased liver could not store or utilize the entire amount. The exact role of the liver in the metabolism of proteins is not well understood. Mann has shown that on removal

of the liver there is a decrease in the amount of urea in the blood. Unfortunately there is as yet no method of measuring accurately the amount of bile salts in the blood. The 3.5 per cent of patients with obstructive jaundice, who die after operation die in most instances from a terminal renal insufficience, due to failure to relieve the common duct obstruction adequately at operation. A few of this group, however, do not die from terminal renal insufficiency, but from a syndrome, which Parham described as hepatic insufficiency. The Rowntree-Rosenthal test of hepatic function (tetrachlorphthalein test) and the van der Bergh test of the amount of bile pigments in the blood will afford valuable aid in formulating surgical judgment and in managing patients with obstructive jaundice.

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**A Method of Treatment of Fracture of a Single Condyle of the Femur with Displacement Backward of the Distal Fragment to the Popliteal Space.**—SUTCLIFFE (*Brit. Jour. Surg.*, 1925, **12**, 450) believes that an intracapsular fracture of a condyle of the femur can be plated. The method of approach to the joint was justified by the traumatism caused by the accident (incision longitudinal on the medial aspect of the patella). The risk of an open operation was justified by the age of the patient and the importance to him of a sound knee, because of his occupation as a miner.

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**Some Aspects of the Endemic Goiter Problem.**—OLESEN (*Mil. Surg.*, 1925, **56**, 466) says that the effects of goiter are neither definitely known or understood. Consequently it is difficult to convince some persons that interference is required. Properly directed study will certainly throw much light upon this important phase of the endemic goiter problem. The treatment of goiter with iodin is neither invariably successful nor easy. In many instances of uncomplicated endemic goiter, the results are decided and gratifying. It is important that physicians acquaint themselves with the most approved methods of treating the condition and acquiring a wholesome respect for the potency of iodin. Kimball's caution that iodin be prescribed in milligrams, rather than grams, and that the toxicity of the element be considered akin to that of arsenic, is a timely admonition. It should be recalled that iodin in the form of Lugol's solution is now being extensively used, in accordance with Plummer's suggestion, in combating the crises of exophthalmic goiter and in preparing these patients for operative procedure.

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**Syphilis of the Stomach.**—HARTWELL (*Ann. Surg.*, 1925, **81**, 767) states that Chiari, in 1891, emphasized the rarity of syphilis of the stomach as demonstrated by histologic evidence. He could find only seven reported cases that he was willing to accept as beyond question. Syphilis produces actual changes in the stomach. They may be direct or indirect. The first are gummatous or simply inflammatory infiltration. Gumma may occur in both hereditary and acquired syphilis. The infiltration was seen only in the former. The indirect results due to syphilitic changes in other organs, for example in the liver or in producing the hemorrhagic diathesis, so called hemorrhagic syphilis, are relatively frequent. Gumma always apparently first starts in the submucosa

and extends from there into the other coats. Through the breaking down of the gumma, particularly because of the action of the gastric juice, ulcer and ultimately scars may form. Then only by the finding of other gummata or the remains of gummatous tissue can the syphilitic nature be established.

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**Tuberculoma of the Cecum.**—HERRICK (*Ann. Surg.*, 1925, **81**, 801) declares that there occasionally occurs in tuberculous patients a tuberculous process localized chiefly in the cecum or colon and characterized by a predominance of scar tissue and round-cell infiltration to a degree closely simulating new growth. This process has been called hyperplastic tuberculosis, but recently authors agree on the term of tuberculoma as more descriptive. It is apparently noted more commonly in the pathologic than the surgical department. By causing chronic incomplete ileus this condition may produce a major handicap in the recovery from pulmonary tuberculosis. The chief errors both in preoperative and operative diagnosis are, calling it appendicitis in young adults or cancer in middle or later life. Incomplete or complete ileus may furnish the first definite symptoms. In several classical cases and some reported more recently, histologic differentiation was difficult or impossible. In young adults, simple exploratory operation or an exclusion anastomosis has been followed by excellent results. Resection is preferable in good surgical risks. In an old patient where differentiation from cancer can be made, an exclusion anastomosis is preferable.

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**The Cancer Problem.**—GROOVER (*South. Med. Jour.*, 1925, **18**, 245) says that the wide discrepancies indicate that no one knows the real truth as to the surgical curability of cancer of the breast and this is also probably true with respect to all cancers. The knife has been the most commonly used instrument for that purpose and with the elaboration of surgical technic more and more tissue has been removed with the hope of attaining that objective. The limit in this direction has probably been reached and little is to be expected from a further elaboration of surgical procedure. A conservative plan of treatment gives promise of reducing practically to a minimum the present operative mortality, of saving patients an appalling number of unnecessary operations and of saving considerable added suffering following many of these operations. In radium- and roentgen-ray therapy, it is probable that the destructive action contributes in a considerable degree to the success obtained in the treatment of superficial cancers, particularly those of the basal-cell variety and this action is also operative in the radium treatment of cancer of the uterus and other tumors where it is possible to bring this substance into intimate contact with the growth by implantation or otherwise. With the advent and use of high voltage roentgen rays, there is a growing feeling among radiologists that the idea of being able to deliver a lethal dose to malignant processes, regardless of type and location is wholly misconceived. The goal of radium therapy should be not only to destroy cancer cells and restrain their activity, but to conserve and if possible activate the natural resistance to cancer invasion. The author has felt that a combination of two unrelated methods of treatment for any disease did not, as a rule, stand the test of experience and farther expressed the belief that a combination of

radiotherapy and surgery in the treatment of cancer would ultimately prove no exception to this rule. It is somewhat significant that surgeons and radiologists are now fairly well agreed that in the treatment of cancer of the uterus, it is best either to irradiate or to operate and not to do both. It is not unlikely that a similar conclusion would be reached with respect to all cancers, regardless of location were they to be subjected to the same comparative studies.

## PEDIATRICS

UNDER THE CHARGE OF

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**A Study of Thymus Glands.**—BLISS (*Arch. Pediat.*, 1925, **42**, 213) studied 1400 newborn infants, and in this number found 70 cases of what he considered dangerously enlarged thymus glands. Many investigators report that an apparently so-called enlarged thymus, which can be shown by percussion and roentgen-ray plate, is very common. The function of the thymus has not been proven. Presumptive evidence classes it with the endocrines. The topography of the thymus lends evidence to the view that part of the symptomatology may be of pressure origin. In the majority of cases a dangerously enlarged thymus presents a definite symptomatology. All apparently so-called enlarged thymus glands do not have symptoms. So-called enlarged thymus glands without symptoms are not considered dangerous. The normal for thymus gland for a baby of a give size, age and weight has not been established. The cause of thymic death has not been proven. The term symptom-producing thymus is preferable to enlarged thymus. Roentgen-ray treatment is efficient and not attended with danger. Only enough of this therapy should be used to relieve symptoms. Thymectomy has been recommended by many authors, but as a therapeutic agent it has been abandoned because of the technical difficulties encountered, and the high mortality. Radium treatment has been found to be efficient but expensive and dangerous. The roentgen ray has the advantages of cheapness and freedom from danger, although there is some question in his mind as to the danger of the roentgen rays to contiguous structures. In competent hands the danger is minimized. With the proper filters the surrounding tissues can be protected. It is said that the size of the dose required to reduce the thymus is not strong enough to be detrimental to the contiguous tissues. The lung and bronchial tissues cannot be injured by the roentgen ray.

**Effects of Radiations of Cod Liver Oil.**—MANVILLE (*Jour. Am. Med. Assn.*, 1925, **84**, 1401) thought that the reason that rats failed to develop infections when raised on diets containing the fat-soluble

vitamins was the bactericidal radiations that are now known to characterize such fats. In order to prove this hypothesis bacterial cultures were exposed to cod liver oil. During the exposure the cod liver oil, rendered alkaline, was oxygenated. This method has been shown to increase the ultraviolet radiations. The results of these experiments strongly indicate an inhibitory action of cod liver oil on bacterial growth. A still further action of cod liver oil and such foodstuffs is seen in the effect the active principle has on cell activity. In the absence of this stimulating influence the cell remains in a quiescent or resting state. This seems to indicate that the cell is depending on this influence for the initiation and maintenance of those processes necessary for its normal activity. Normal body functions require that there be enough of this stimulating influence present to act on all the cells in proportion to their needs. Anything less than this results in a corresponding decrease in cell activity. A slight excess may result in an increase above normal; but when a marked excess is present stimulation is replaced by inhibition, if not by actual destruction. Cell activity is manifested first by multiplication, either for growth or for maintenance, and second by normal secretory activity necessary for adequate digestive processes, resistance to infections and general well-being. It will thus be seen that the results of an experiment will depend on the time in an animal's life during which the test diet is fed. When a deficient diet is fed to an immature animal growth will be stopped, the secretions will be curtailed, the reproductive organs will remain infantile and the animal will finally die of undernutrition and the effects of decreased resistance to infections. If a similar diet is fed to an adult animal its normal functions must be carried on by the residual vitamin its body has stored. As this becomes depleted the first function to be lost is reproductive ability. Further evidences of the gradual depletion of this reserve are manifested by an increasingly evident appearance of ill-being. On the other hand, when the diet contains an excess of this active principle the most marked result is sterility. As with the roentgen ray and radium, the effect of the radiations seems to be selective, the cells undergoing the most rapid cell division being the most affected. Beside the action of cod liver oil in curing or preventing rickets, we are led to conclude from the foregoing that there are two other specific actions: A stimulation of cell activity and a distinct inhibitory effect on bacterial growths; when these active substances are in excess of the amount producing stimulation there is exerted a depressing action, the most striking manifestation of which is a lack of fertility. The separation of fat-soluble A into two separate vitamins, each with a specific action, does not seem justified when the effects can be explained as being due to different concentrations of the same principle.

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**Skin Test for Susceptibility to Scarlet Fever.**—Dick and Dick (*Jour. Am. Med. Assn.*, 1925, **84**, 1477) have not observed any bad effects from immunizing doses. No necrosis, sloughing or secondary infections have occurred; nor have they observed any harmful effect on the heart, kidneys or other organs. The reactions that occur are either local or general. There is nearly always some local reaction at the site of the injection. It consists of swelling and reddening, which

appear within a few hours and begin to subside in from eighteen to forty-eight hours. The intensity of the local reaction varies with the susceptibility of the person. There may be some desquamation over the area of skin involved. General reactions, if they occur at all, seldom follow any but the first dose. They are comparatively uncommon with the dosage mentioned. They usually consist of some general malaise. Light and transient scarlatinal rashes may follow the first dose in highly susceptible persons. Lowering the dosage does not completely eliminate the possibility of a rash. Nausea of a few hours' duration is still less frequent than the rashes. The most marked general reaction has subsided in forty-eight hours, without having any after effects. Persons who have a general reaction following the first dose do not usually have any general reactions to subsequent doses. None of the reactions are so severe as those that occur during the course of immunization to either typhoid or diphtheria. If properly graduated doses of toxin are employed general reactions may follow any doses that are disproportionately large. The passive immunity conferred by prophylactic doses of scarlet-fever antitoxin is immediate, but transient. It lasts from four to eight weeks. The after-immunity produced by injections of graduated doses of scarlet fever toxin is acquired less promptly but is more permanent. Retests after immunizing doses of scarlet-fever toxin, made at intervals of from three days to one year in a series of 1634 susceptible persons have shown that immunity develops within one or two weeks. Retests have been made at intervals of one month, two months, six months and one year in persons who had been incompletely immunized with scarlet-fever toxin, so that two weeks after the last dose their skin reactions were modified but not negative. In none did the partial immunity progress to complete immunity. Before they were assigned to the care of scarlet fever patients 206 susceptible nurses were immunized to the point of a negative skin reaction. Their exposure was the same type and duration as that encountered by the nurses who had spontaneously negative skin reactions. None of these nurses, whose skin tests had been rendered negative by active immunization, contracted scarlet fever. In another series 405 susceptible persons completely immunized with scarlet-fever toxin there were no cases of scarlet fever. The exposure of these persons was direct but less protracted than that of the nurses, and many would doubtless have escaped infection without any preventive measure. Groups of persons with positive skin reactions were immunized to the points of completely negative reactions, and retested at intervals of three months, six months, one year and one and a half years. In each case the retests were negative.

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**Rheumatic Infections in Childhood.**—COATES (*Brit. Med. Jour.*, 1925, **1**, 550) thought, while subcutaneous rheumatic nodules usually make their appearance only in grave cases associated with gross cardiac disease, nodules less obvious than those of graver infection might be discovered in subacute cases. This suggestion was established in part by the examination of children known to be suffering from rheumatic infection. He examined 100 children between the ages of two and twelve years for subcutaneous nodules, irrespective of the complaints for which they were brought to the hospital. In searching for the

nodules particular attention was paid to the spinous processes of the vertebræ and to the olecranon processes. The nodules appeared to vary in size from that of a small sago grain to that of a pinhead and were often in small clusters. Synovitic creaking was often obvious around the vertebral spines, and is most characteristic. Of the 100 children 23 gave a history suggesting rheumatic infection, and in these no other causes of a toxic state could be elicited, except Ascaris lumbricoides in two instances, efficient treatment of which did not alleviate the symptoms.

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**Acute Nephritis in Children.**—ALLISON (*Practitioner*, 1925, **114**, 222) investigated 12 cases of acute nephritis in children, ranging in age from four to eleven years, in an attempt to discover the etiologic factors, to study the clinical course of the disease and to ascertain the after-effects. Two-thirds of the cases at the time of the onset of the illness showed markedly enlarged tonsils and adenoids, which were in a state of chronic inflammation. From the results of their removal, he was convinced that these were the etiologic factors. Clinically half of the cases showed passive hematuria, sever constitutional disturbances and slight edema. Smoky and dark concentrated urine was associated with less severe constitutional disturbance. Oliguria was not a feature in any of the cases. The functional tests were of no prognostic or diagnostic value. The blood urea was raised in one-third of the cases, the rise being temporary, and returning to normal with subsidence of the acute symptoms. The large majority of patients were free from symptoms and had apparently recovered within a month of the onset. No cases of uremia or a fatal termination were encountered. The children were reëxamined at periods ranging from nine months to a year, and were found to be healthy and to show no trace of disease.

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## DERMATOLOGY AND SYPHILIS

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**The Wassermann Test on the Blood Serum of Pregnant Women.**—D. L. BELDING (*Am. Jour. Syph.*, 1925, **9**, 132). Fetal (cord) blood gives a lower percentage of positive reactions than the maternal blood. Approximately one-third of the cord bloods of serum-positive mothers gives a positive reaction. The reaction in the cord blood is not a cri-

terion of the future reaction in the child since both positive and negative cord reactions ultimately may show the reverse in the child. Because of its weak reaction and unreliability in prognosis and because it does not permit antipartum treatment, the cord blood is unsatisfactory for routine Wassermann tests in maternity hospitals. From 25 to 30 per cent of positive reactions which occur in the sera of pregnant women are the result of technical errors from anticomplementary sera or from nonsyphilitic-fixation substances. Repeated tests of serum from pregnant women which show many transitions from positive to negative and *vice versa* furnish circumstantial evidence of nonsyphilitic fixation. A Wassermann reaction during pregnancy which varies from positive to negative may occur in true syphilis. In nonsyphilitic pregnant women a variable positive reaction may result from the anticomplementary action of the serum and nonsyphilitic fixation. As a rule these reactions are weaker and more fleeting than the syphilitic positives but no means of differentiating between syphilitic and nonsyphilitic fixation in weakly positive cases is known.

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**The Treatment of Psoriasis by Intravenous Injections of Salicylate of Soda.**—SMITH (*Brit. Jour. Dermat. and Syph.*, 1925, **37**, 33). Intravenous injections of sodium salicylate caused the disappearance of the psoriatic eruption in 16 per cent of 57 cases, its almost complete disappearance in 18 per cent, a distinct improvement in 14 per cent. Fifty-two per cent were either unimproved or worse. A maximum dose of 3.0 gm., 20 per cent solution in distilled water, was given twice weekly. Exfoliative dermatitis ensued in 6 per cent of the cases. Several difficult cases, including one which had resisted a great variety of measures, were cleared by this means. No evidence is shown of its power to prevent relapse. It is considered advisable to combine it with local treatment, which was omitted in the above series solely to evaluate the method.

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**Benign Lymphogranuloma and its Nature.**—JORGEN SCHAUMANN (*Brit. Jour. Dermat. and Syph.*, 1924, **36**, 515) states that lupus pernio and Boeck's sarcoids are identical and that these dermatoses are manifestations of benign lymphogranuloma. Benign lymphogranuloma may be present without skin manifestations. The systemic involvement occurs in the lymphatic system as shown by the presence of typical tubercles in the tonsils, frequent enlargement of the spleen and an abundant pulmonary infiltration shown only by radiography. There is a predilection of the disease for the hematopoietic system and the bone marrow is practically always involved. These medullary lesions are much more extensive than radiography would lead one to believe. A normal radiologic condition of the bones does not eliminate the presence of the medullary lesions, nor indeed even the possibility of a complete granulomatous transformation of the osseous medulla. He states that the disease is caused by the tubercle bacillus and probably by its bovine variety, though it does not present the accepted criteria of tuberculosis. The tuberculin test in active lymphogranuloma is negative. The patients frequently later become the victims of classical tuberculosis, the tuberculin reaction becoming positive and the tubercle bacillus no longer produces lesions of the lymphogranulomatous type

but classical tuberculous lesions. There is a singular immunity against tuberculosis until this change occurs. The granulomatous process disappears under the influence of developing tuberculosis. The cutaneous manifestations of lymphogranuloma are tumors, erythrodermia and prurigo, urticaria and other slight eruptions. The tumors are of the following types: Besnier's lupus pernio, Boeck's cutaneous sarcoids of the nodular, diffuse infiltrated or disseminated miliary types. The erythrodermias consist of patches of scaly redness of considerable extent and persistence in association with the systemic findings of lymphogranuloma. The author has established a symptomatic triad for the diagnosis of lymphogranuloma, consisting of histologic examination of the tonsils for evidence of granulomatous invasion; second, radiographic examination, particularly of the fingers and toes for medullary involvement; third, a negative tuberculin reaction. Hutchinson's chilblain lupus, subcutaneous sarcoid of Darier, granuloma annulare, lupus vulgaris and classical tuberculids do not belong in the group with lymphogranuloma as proved by absence of involvement of the hematopoietic system and a positive tuberculin test. The author does not believe that lupus vulgaris or tuberculids can coexist with the manifestations of lymphogranuloma despite reports in the literature of this combination.

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## GYNECOLOGY

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**Nonoperative Treatment of Ureteral Calculus.**—Some years ago a diagnosis of ureteral calculus usually meant that early operation was indicated, but with a more careful study of the possibilities of spontaneous passage of many of these stones conservative surgeons began to recommend watchful waiting in many of these cases. As cystoscopic technic improved, there has been an associated increase in the number of nonoperative procedures which have been recommended to favor the passage of these calculi. According to BEER and HAHN (*Jour. Am. Med. Assn.*, 1925, **84**, 1028), the open operation is definitely indicated for some stubborn stones that do not respond to cystoscopic methods, especially the impacted stones that completely block the ureter, the large stones, the stones that do not move after repeated attacks of colic and those stones associated with severe uncontrollable infection of the kidney. There are, however, good reasons for avoiding open operation, whenever there is a good chance of ridding the ureter of the stone by a simpler method. They call attention to a method which they have been using and which they believe should

be used more often by the profession, especially when the calculi are in the lower half of the ureter. The method consists simply in passing a catheter beyond the stone and allowing it to remain there for from two to five days. This procedure may result in the passage of the calculus within a few hours after withdrawal of the catheter. The mechanism is not clear. Perhaps the edema of the mucous membrane which holds the stone is allowed to subside; perhaps some traction on and dislocation of the stone are caused by withdrawal of the catheter; perhaps dilatation of the ureter is the chief factor. Whatever the mechanism, it has two great advantages over other methods in this category: (1) A single treatment frequently suffices to deliver the stone, and (2) stones are passed with very little pain. Of the 27 cases in which it was tried by the authors, the diagnosis of stone was very doubtful in 1 case. Four additional cases were not favorable for the use of this method, the stone being rather large or high up in the ureter. Of 22 cases in which this method might seem to have been indicated there were 10 proved successes, or 45 per cent. Two additional patients almost certainly passed the stone in the hospital, as evidenced by cystoscopic findings before and after, but as the stone was not recovered these are not included in the 10 successes. Two other stones were passed after discharge from the hospital. In other words, out of 22 cases probably 14 successful deliveries were obtained (60 per cent). The usefulness of the indwelling catheter is emphasized by comparing their recent results with the results obtained before the adoption of this method. In a series of 114 cases definitely diagnosed as ureteral stone, 23 stones, or 20 per cent, were passed at or following cystoscopic manipulation. In this series of 114 cases occurring before the indwelling catheter was used 76 were favorable cases, and 23 stones, or 30 per cent of these, passed following one or more cystoscopic manipulations. Thus, there is a definite gain of from 50 to 100 per cent by the use of the indwelling catheter over the other cystoscopic methods they have used. It should be remembered that this method is useful only for the smaller or medium sized stones, particularly those in the lower half of the ureter. The method is practically harmless in the hands of the trained cystoscopist. Another new nonoperative method has been devised by Illievitz (*Surg., Gyn. and Obst.*, 1925, **40**, 575) based on the dilatation of the ureter with air. He has constructed a catheter with a thin rubber bulb over the end, which can be inflated by means of a syringe at the other end. In the course of his experimental work the catheter was inserted into the ureter near the stone, and after repeated inflations of the catheter and gradual withdrawal of it the stone seemed to follow it downward. At the wall of the bladder, where a stone tends to become lodged, the inflations were repeated several times, and the last time the catheter was withdrawn quickly in the partially inflated condition. The stone invariably followed the catheter into the bladder. This method has not as yet been tried on the human, but the author suggests that the ordinary dental chair or operating table with stools for the feet, with the patient in the sitting position, will make it possible for the stone to come down by gravity during dilatation.

**Correlation of Uterine and Tubal Changes in Tubal Gestation.**—It has long been known that the occurrence of tubal pregnancy calls forth a more or less marked decidual reaction on the part of the uterine mucosa. There is, however, no unanimity of opinion as to the correlation of these uterine changes with those noted in the pregnant tube and with the clinical symptoms presented by the patient. In order to throw some light on this subject, NOVAK and DARNER (*Am. Jour. Obst. and Gynec.*, 1925, **9**, 295) have presented a paper based upon the study of 21 cases of tubal pregnancy in which, in addition to the tubal gestation sac, the uterine mucosa was available for study, thus affording an opportunity of correlating the uterine and tubal changes in this connection. In 15 cases the uterine mucosa was available because a hysterectomy had been done, in 3 because a preliminary curettage had been performed and in 3 because a more or less perfect uterine cast had been expelled by the patient. The decidual reaction occurring in the uterus with extrauterine pregnancy is found to be identical with that of normal gestation so long as the embryo is alive. With the death of the latter, however, the superficial compact portion, with at times a considerable portion of the spongy glandular layer, is cast off. Its expulsion from the woman's vagina, however, may not take place for a considerable period, perhaps many days, after its separation from the deeper layers. The mechanism of the separation is strongly suggestive of that observed in connection with the throwing off of the corresponding portions of the endometrium in the nonpregnant woman at the time of menstruation. The same statement applies to the process of regeneration. In view of the degenerative and autolytic changes involving the sequestrated decidua, it is not infrequently thrown off in smaller particles rather than as a large cast of the uterine cavity. They have found no evidence that the decidua merely involutes or shrinks, without loss of tissue, as has been claimed by some observers. The overwhelming majority of cases of tubal pregnancy come under observation only after the death of the embryo, and in these cases the endometrium has retrogressed from its originally decidual character. The microscopic examination of uterine curettings in such cases is of very little diagnostic value. On the other hand, the histologic study of the uterine mucosa in those cases where the pregnancy is still developing actively shows a typical decidual reaction. When curetting in a doubtful case yields such a mucosa without villi, the information gained is very valuable, though not conclusive. Unfortunately, however, cases of this type are curetted far less frequently than those of the other group, for they are characterized clinically by amenorrhea, with the possibility of intrauterine pregnancy. Decidual reaction in the tubal wall occurs in at least a fraction of the cases. It is never in any way comparable with that seen in the uterus, beings usually patchy in its distribution. Mistakes in the diagnosis of decidual tissue in such cases are frequent, for a pseudodecidual picture is common in the connective tissue from simple hyperemia or edema. Moreover great care is necessary to avoid mistaking for decidua the trophoblastic cells which invade the tubal wall so widely. In certain cases, however, the morphology of the cells is so typically that of decidual cells, their distinctness from the gestation site is so clearly discernible, and their derivation from the connective tissue so definitely

suggested by the presence of transition stages, that the diagnosis permits of no doubt. Furthermore, the occurrence of certain cases in which the reaction is noted in the nonpregnant tube of the opposite side is even more convincing. Finally, attention has been called to the not infrequent finding of islands of "ectopic decidua" on the ovary, the posterior surface of the uterus and many other locations in the pelvis, and the suggestion is offered, without as yet any definite proof, that there may be some connection between such decidual islands and the "endometrial implants" described by Sampson. The latter, it will be recalled, have pretty much the same distribution as that of ectopic decidua.

## RADIOLOGY

UNDER THE CHARGE OF

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**Radiographic Findings in Hepatic Abscess, Amebic Type.**—J. C. DICKINSON (*Radiology*, 1925, **4**, 273) reports four cases with a diagnosis of abscess in the right lobe of the liver, amebic in type. The best method of examination is with the fluoroscope, which shows the right diaphragm to be elevated and its excursion limited or absent. The right costophrenic angle is increased in acuteness and if the abscess is near the superior surface of the liver, a rounded elevation can be seen in the diaphragm. The whole liver shadow is enlarged. If the abscess ruptures into the pleural cavity, the picture may be that of a pleural effusion. If this results in an empyema differentiation may be impossible until the pleural cavity is drained. If it has ruptured into the lung, localized consolidation followed by expectoration of amebic pus is quite characteristic. In a certain proportion of cases there is a characteristic collection of gas between the dome of the liver and the diaphragm.

**Roentgenotherapy of Vascular Nevi.**—Unfiltered rays of medium penetration (5 to 6 Benoist) in moderate doses (never exceeding 4H) given at three sittings with an interval of three or four weeks will give good results in vascular, tuberous nevi, according to F. BARJON (*Jour. de Radiologie et d'Elect.*, 1925, **9**, 15). Only tuberous nevi should be thus treated; one should never apply radiotherapy to flat nevi. Treatment should begin early, preferably in the first six months of age. In all cases there is a disappearance of the tumor and the discoloration, and in favorable cases the esthetic result approaches perfection.

**Diagnostic Pneumothorax.**—Pneumothorax is a valuable aid in the diagnosis of thoracic pathology, especially pathology of the mediastinum, pleura, lungs, ribs, and the chest wall, according to HARRY J. ISAACS (*Am. Jour. Roentgenol. and Rad. Ther.*, 1925, **13**, 3). Diagnostic

pneumothorax is especially indicated in lung tumors. If the injection of air into the pleural cavity causes a complete separation of the lung from the costal pleura, it speaks for a lung tumor, while extensive adhesions (failure of lung to collapse) speaks more for an interlobar empyema with pleural thickening. The same technique as for therapeutic pneumothorax is used. Complications reported in the therapeutic work are pleural shock, perforation of lung, infection, pleural effusion, air embolism, and subcutaneous edema, but are very rare. Of the 2 cases reported by Isaacs, the roentgen-ray report of the first described a large shadow occupying the left lung filled from apex to ninth rib, posteriorly, with left apex and the mediastinum obscure. After injection of 650 cc of air the radiograph showed a tumor mass well defined. The lung tumor, diagnosed as sarcoma, decreased considerably after roentgenotherapy. In the second case the roentgen-ray report described a dense shadow in the right side of chest from clavicle to sixth rib, regular in outline and irregular in density, merging with the cardiac shadow after injection of 650 cc of air the radiograph showed a compression of the lung and complete separation of the pleura from the lung tissue. Diagnosis of primary pulmonary malignancy was made.

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**A Congenital Anomaly of the Patella.** Separation of a piece or pieces of bone from the patella as a congenital anomaly is frequently misinterpreted as fracture of the patella, according to A. W. GEORGE and R. D. LEONARD (*Am. Jour. Roentgenol. and Rad. Ther.*, 1925, **13**, 3). In six cases they have found the fragment or fragments in the upper outer quadrant of the patella, being smooth in outline, and having a periphery of cortical bone. Usually the deformity is present in both patellas, therefore, the opposite patella should always be roentgenographed in case of abnormality of one. Failure to make correct diagnoses in these cases has caused insurance companies to pay compensation for many weeks, believing the patient to have a fractured patella.

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**Further Experience with Tetrabromphenolphthalein Sodium Salt in the Roentgenologic Diagnosis of Gall-bladder Disease.**—The intravenous injection of tetrabromphenolphthalein sodium salt is of value in roentgenographic examination of the gall bladder according to W. H. STEWART (*Am. Jour. Roentgenol. and Rad. Ther.*, 1925, **13**, 3), because it is a method that outlines the gall bladder, showing its size, shape, emptying power and the presence of gall stones. An ampule of 5.5 gm. of the salt is dissolved in 40 cc of freshly distilled water by heating and administered intravenously in two doses, 20 cc first and repeated in a half hour. The toxicity of the salt, few patients escaping its unpleasant reactions, is the chief objection to this method of gall-bladder diagnosis and special attention to its prevention has been given by Stewart. Contraindications are cardiac patients, diabetics, and those suffering from severe constitutional diseases. Highly emotional and neurotic patients should be avoided. Best results have been obtained by a thorough cleansing of the intestinal tract, besides a starvation diet on the day before administration, then a hypodermic injection of fifteen minutes of adrenalin (1 to 1000 solution) a half hour before the first intravenous injection. Although the reaction has been very severe in some cases there have been no deaths from this preparation. Films

are made at eight, twelve and twenty-four hours after administration of the dye. In 36 cases checked up by operation, Stewart has found that deformity and malposition of the gall bladder usually indicates disease, and that if no shadow is obtained it is due to one of the following reasons: (1) Obstruction of the cystic duct; (2) contents of gall bladder do not mix with the dye; (3) too little bile to cast a shadow; (4) too much content diluting the dye, and (5) poor liver function.

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**The End Results in Roentgen-ray Treatment of Cutaneous Cancer.**—In a series of 144 selected patients with skin cancer 93.6 per cent cures were obtained with roentgen-ray treatment by H. H. HAZEN and E. R. WHITMORE (*Am. Jour. Roentgenol. and Rad. Ther.*, 1925, **13**, 2) or 96 per cent cures of 225 selected growths. Skin cancer is more common in men and the results are better in women. Deep ulcers and nodules are not as favorable as other types; also, growths of the ear and in cartilage give poor results. The age of the patient does not affect the result materially but early lesions give better results than old, and small lesions better than large. The roentgen ray gives the same results as radium and surgery, but cases previously irradiated gave only 50 per cent cures. The authors have found a one-and-a-half-unit dose as effectual as a two-and-a-half-unit dose, giving at least three or four treatments to all cases or more if necessary. They found that 94 per cent of the recurrences appear in the first year and that the causes of failure are deep invasion of cartilage, poor coöperation, localization in scar tissue and previous radiation. Prickle-cell cancers resulted in 45 per cent cures and of cancerous glands, 41 per cent cures. There are a number of theories of the mechanism of cure of skin cancers and the view held by the authors is that the cure of cancer depends upon a proper stimulation of tissue reaction and that the mode of action of irradiation is through its effect upon the healthy tissue, not upon the cancer.

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**Value of Radium and Roentgen Radiation in the Treatment of Benign Uterine Hemorrhage.**—Benign uterine hemorrhage, from the standpoint of treatment with radium and roentgen radiation can be divided into four classes according to HARRY E. BUNDY (*Am. Jour. Roentgenol. and Rad. Ther.*, 1925, **13**, 2), namely, fibroids, essential menorrhagia, bleeding following inflammatory adnexal disease, and pernicious bleeding during gestation. Small fibroids should be treated with radium; those the size of a first trimester pregnancy respond best to roentgen radiation or a combination of radium and roentgen ray; while larger fibroids should be treated surgically if possible. The danger of producing a menopause should always be borne in mind. The author has been using in young women 300 to 600 mg. element hours, repeating if necessary. Essential menorrhagias respond very readily to the radium rays. The bleeding from adnexal disease, often quite intractable to ordinary forms of treatment, has yielded quite uniformly to roentgen radiation over the spleen. The author has also adopted this radiation for pernicious bleeding of gestation, and has had good results in all but 4 cases out of 33, using a 15 per cent dose delivered to the spleen, repeated in forty-eight hours if hemorrhage persists, giving then a two-thirds erythema skin dose.

# PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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**An Exotic Strain of Encephalitogenic Virus.**—A virus obtained from the cerebrospinal fluid of a patient suffering from vascular and neural syphilis, and who never presented symptoms of epidemic encephalitis, is described by FLEXNER and AMOS (*Jour. Exper. Med.*, 1925, **41**, 215). This virus is indistinguishable from the so-called virus of encephalitis on the one hand, and from the virus of febrile herpes on the other. Hitherto, these two viruses have been described as the encephalitis-inducing agents. This work lays the conclusions from all preceding studies open to question. Specimens of cerebrospinal fluid numbering 100 were used in the investigation, of which 27 were derived from patients diagnosed or suspected as being cases of epidemic encephalitis, and 73 from cases of a miscellaneous character. Of this series, from only 1 was a virus obtained (known as their "J. B." virus) which was capable of producing experimental encephalitis in rabbits, and this, as noted above, was from a case of syphilis. Inoculations were made into rabbits by the following routes: Intracranial, corneal, skin, blood, nasal and testicular. Type protocols are given in each instance. Throughout these procedures the "J. B." virus demonstrated its potency and its close relationship to the previously described encephalitis-producing viruses. In reviewing the histology of "virus encephalitis" the authors report a marked disparity in the findings, these being due in great part, they suggest, to the mode of inoculation in which several factors may coöperate; trauma, positively chemotactic tissue elements and virus. Furthermore the rabbit itself very often exhibits, even in health, a variety of encephalitis, a factor which may have misguided some investigators. In studying the cerebrospinal fluids derived from the 27 cases of suspected epidemic encephalitis they failed to produce the disease or to confirm the results obtained by other workers. They conclude that their "J. B." virus is, in reality, a herpes virus that found its way into the cerebrospinal fluid. They also make the suggestion that all viruses hitherto described are of the same nature, thus making the etiology of epidemic encephalitis entirely unresolved, and that to ascribe the disease to the herpes virus is, they believe, at the present time entirely unwarranted.

**Herpetic Strains of Encephalitogenic Virus.**—In this paper FLEXNER and AMOS (*Jour. Exper. Med.*, 1925, **41**, 233) endeavor to demonstrate the similarity of the encephalitis virus to that of febrile herpes. A somewhat similar idea has been offered by Levaditi, Nicolau and Poincloux, who, however, merely suggest the name of "herpetico-encephalitic" virus to embrace a group of viruses of which a neuro-

tropic variety constitutes the provocative virus of epidemic encephalitis. Furthermore, in order to produce this disease in man a mass modification of the soil (nervous system) and the prevalence of this specially adapted virus are necessary. To the conjunction of these two factors is ascribed the several outbreaks of epidemic encephalitis in many parts of the world in the past few years, and this explanation of the etiology is questioned by the authors of the present paper. Several strains of the virus of febrile herpes were used in the experiment, of which one, the "H. F.," was principally studied. It was taken from a fresh herpetic vesicle on the lip of a subject very prone to attacks of febrile herpes. This strain was capable of producing typical symptoms of "virus encephalitis" in rabbits, to which they succumbed. The strain was studied for a period of three years, during which time it was compared with the "J. B." virus previously described, the Levaditi virus *souche* C., the Doerr and Basel virus and the Goodpasture strain, Micrococcus virus. Illustrative protocols are given of rabbits inoculated by the intracranial, corneal, skin, nasal, intravenous and intratesticular routes. Guinea pigs, rats and mice were also used in the study with some modifications of the findings. They find that the "H. F." strain exhibits a degree of encephalitogenic power not exceeded and rarely equalled by any strain of the so-called encephalitis virus, and "virus encephalitis" invariably follows inoculation by any of the routes described. The virus is also glycerol-resistant, is filterable through Berkefeld candles and behaves immunologically as do the usual strains of herpes and encephalitis virus. They conclude that the encephalitogenic power is not a special property of virus secured from cases of epidemic encephalitis, and that different properties, such as dermatotropic and neurotropic, may be ascribed to differences in potency.

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**The Pathology of the Hypophysis.**—This is the first of a series of studies on the pathology of the hypophysis and deals with the presence of abnormal cells in the posterior lobe. For some years past SIMONDS and BRANDES (*Am. Jour. Path.*, 1925, **1**, 209) have made serial sections of all hypophyses removed at necropsy. The groups of cells are fairly well circumscribed, nonencapsulated masses of cells varying in size from less than 0.25 mm. to 1 mm. in diameter. They are located in the posterolateral quadrants of the neurohypophysis, and are in general similar to those reported by Sternberg and by Priesel. The cells are large, round, oval or polygonal cells which stain a bluish purple and have abundant granular cytoplasm. The nuclei are round and usually placed eccentrically. Frequently they are deeply stained and pyknotic, or they may be pale and apparently undergoing karyolysis. Some of the cells are devoid of nuclei; others show shadowy nuclear remains. No nucleoli were seen within any of the cells. The stroma was scanty and similar to that of the posterior lobe. The total quantity of blood-vessels within these areas is very small. The authors are not convinced that these masses of cells are true neoplasms, but without being dogmatic they believe rather that the lesion is a localized retrogressive change in the glia cells to which they relate the large cells of this lesion because many of the cells give off from their surfaces fine branching processes which take part in the formation of the inter-

cellular fibrillar meshwork. They point out that the lesion is found more commonly in the later decades of life. Moreover some of the cells in these lesions are undergoing degeneration or even necrosis, as evidenced by the character of the cytoplasm and of the nuclei. While the cell masses are minute they occupy a relatively considerable proportion of the neurohypophysis and may consequently produce some alteration of its function. The clinical notes in the cases they reported were incomplete and failed to disclose any of the functional or bodily changes usually ascribed to lesions of the hypophysis, but they point out that a more careful study of the patients with this pathological process in mind may reveal some clinical manifestation ascribable to it.

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**Concerning the Microscopic Structure of the Hypophysis Cerebri in Acromegaly.**—In the belief that, if acromegaly is a disease entity, the adenomatous change which takes place in the hypophysis should show constant histological characteristics, BAILEY and DAVIDOFF (*Am. Jour. Path.*, 1925, **1**, 185) undertook a critical study and analysis of the material available at the Peter Bent Brigham Hospital. They recommend fixation of the hypophysis cerebri in Regaud's fluid, and for a differential stain to demonstrate the *a* and *b* granules they prefer the acid fuchsin-acid violet method of Bailey. They point out in detail the errors of interpretation that may arise from other methods of fixation and staining. The report is based upon a study of the tissues removed at operation from 35 patients with symptoms of acromegaly. Four of these cases are reported in detail with plates, including roentgenographs. As a control they also report their findings in 54 cases of adenomatous enlargement of the hypophysis with dyspituitrism but without acromegalic manifestations. In general they found that in cases of acromegaly in which the gland reaches a size sufficient to demand an operation a constant pathological change had taken place in the anterior lobe of the hypophysis. This change consisted of an adenomatous formation composed of cells containing *a* granules. The cells lay in a loose mass practically without stroma and with very little blood supply. The normal columns of cells were wanting. The cells themselves varied greatly in size and some of them contained as many as half a dozen nuclei. Many of the cells tended to flatten along the surface of adjacent cells in the form of crescents. The *a* granules were finer than normal and showed a tendency to collect in the periphery of the cytoplasm. The increase in the *a* granules was definitely present in 31 of the 35 cases studied. In the remaining 4 cases no *a* granules could be proved, but in 3 of them the cells contained coarse granules which were definitely not *b* granules, although they could not be differentiated clearly as the *a* type. In the fourth case a diagnosis of acromegaly was not made at the time of operation, but the patient returned later with characteristic changes and died in diabetic coma. No necropsy was obtainable. On the other hand in the 54 cases of adenomatous enlargement of the hypophysis without acromegalic manifestations practically no *a* granules could be found even after a long search. The cell boundaries were indistinct. The cells were arranged in thick columns separated by sepa of connective tissue. The cells were elongated and of the chromophobe type, having no granules other than mitochondria. Each cell had a simple elongated

nucleus. In addition to these cases they have reviewed the literature including only those cases in which sufficient details of the histological technique were given, so that one could be sure that it was adequate for the demonstration of *a* granules. In all 23 cases were reviewed, and of these 17 definitely showed an increase in the *a* granules. Of the remaining 6 cases, 3 showed an increase of the eosinophilic cells with multinucleation, 2 showed multinucleation, while the sixth presented cells with fine granules, the cells not being arranged in alveoli. They thus believe that in acromegaly there is a definite histological change in the pars distalis of the hypophysis cerebri.

## HYGIENE AND PUBLIC HEALTH

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**Results Obtained with the Dick Test Before and After Immunization with the Toxin of the Hemolytic Streptococcus of Scarlet Fever.**—DYER and SOCKRIDER (*Pub. Health Rept.*, 1925, **40**, 593) tested groups of white and of colored boys in an institution, and found 17.1 per cent to be susceptible to scarlet fever, according to the Dick test. These were immunized by three injections of scarlet-fever toxin and about 80 per cent were rendered negative to a subsequent test with the toxin. The presence of a preservative, 0.5 per cent phenol, seemed to have no adverse influence on the immunizing properties of the toxin. A heated toxin and the medium alone, used as controls of the test, were compared, but without conclusive evidence of the superiority of either.

**Tetanus from Vaccination Dressings.**—The Public Health Service (*Pub. Health Rept.*, 1925, **40**, 559) issues a warning against the use of bunion pads as a dressing in vaccination against smallpox. This singular use of bunion pads appears to be more common than would be supposed. Several fatal cases of tetanus following their use have recently occurred in the United States, and laboratory tests have demonstrated the presence of tetanus spores in bunion pads from the same source as those which were associated with tetanus cases. The Public Health Service deprecates the use of any kind of a shield as a vaccination dressing. The employment of such a shield tends to prevent evaporation, to retain heat, moisture, or discharges, with a consequent softening of the vesicle, to obstruct lymphatic drainage, to

produce hyperemia and to create conditions apparently favorable for the development of bacterial invasion, especially by the tetanus organism. The smallest single site insertion compatible with a successful take and with no immediate dressing whatever is believed to be the best method of vaccination in the majority of cases.

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**Absence of Transferable Immunizing Substances in the Blood of Morphin and Heroin Addicts.**—DuMez and Kolb (*Pub. Health Rept.*, 1925, **40**, 548) review briefly the claims of those who consider that that is an immunological basis for drug addiction. In the authors' experimental work the serum of morphin and heroin addicts was used to determine whether or not it had any protective influence on the effect of doses of morphin or heroin in white mice. In every case the results were negative, that is, no protective influence was manifested by the serum of addicts when compared with that of nonaddicts.

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**Mild Typhus (Brill's Disease) in the Lower Rio Grande Valley.**—Sinclair and Maxey (*Pub. Health Rept.*, 1925, **40**, 241) observed twenty cases of Brill's disease, all of which recovered. The Weil-Felix reaction with B. proteus was positive in the large majority of cases. While the source of the epidemic could not be traced, it was in some instances possible to demonstrate close association between cases. The authors failed to find body lice associated with any case, and state that lice do not thrive in the Rio Grande Valley, at least during the summer months. On the contrary, head lice are common though it is not stated that these were associated with any of the cases.

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**The Incidence of Illness in a General Population Group**—According to Sydenstricker (*Pub. Health Rept.*, 1925, **40**, 279), a population of between 8000 and 9000 was kept under observation for two and a half years, including 1600 families made up of 87,200 white persons for the entire period. The method used was that of house-to-house canvass and the collection of data from collateral sources. The data are summarized as follows: Summary: A true picture of the ill health, and therefore, of the problems to be attacked by those who are engaged in preventing disease, is not adequately portrayed by death statistics. The obvious reason for this is that mortality records by definition do not include the cases of illness that are not fatal, to say nothing of the suffering and the lowered vigor and the lessened efficiency among the living. A study of illness in a general population group in a typical small city not only shows the inadequacy of mortality statistics for this purpose, but suggests the kind of picture that complete morbidity records would afford. Looking at it in broad outline only, it was found in the group of persons studied that: (1) Over 100 cases of illness occur annually for each death. (2) More than half of the morbidity was due to respiratory diseases; the ratio of respiratory illnesses to deaths from respiratory causes was more than 300 to 1. (3) Diseases and disorders of the digestive system caused an annual illness rate of 117 per 1000 but a mortality rate of less than 1 per 1000, a ratio of about 200 to 1. (4) The "general diseases"—epidemic and nonepidemic—composed principally of those diseases against which public health effort has been mainly directed, caused only 11 per cent of all

illnesses. (5) While deaths occur principally in infancy and in old age, ill health, as measured by the incidence of illness, occurs with comparatively little variation throughout life; it is prevalent among the young, those in the "prime of life" and the aged without much discrimination. This picture inevitably suggests a point of attack upon the causes of ill health not adequately recognized now—the diseases which are incident between the extremes of life. If, as it is now the custom, success of public-health work is to be measured in money terms, surely no more cogent argument could be put forward than that of the economy of preventing loss of the efficiency of the population at those ages when health means the most in production. It is not hard to figure that a day of sickness prevented at the age of thirty or forty years is more profitable than at the age of seventy. But, in a broader sense, the diseases which cause ill health are a challenge to the sanitarian, not merely because they have an exhausting effect upon man's power to resist death but because they lessen his ability to achieve and his capacity to enjoy life in the years of his most abundant strength.

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**Studies on the Industrial Dust Problem**—GREENBERG (*Pub. Health Rept.*, 1925, **40**, 292) shows clearly that certain dusty trades result in an excessive prevalence of tuberculosis compared with the population in general. The highest tuberculosis mortality is found in marble and stone cutters, where it reaches 540.5 per 100,000. This is compared with a rate of 236.7 for all occupied males and 111.7 for farmers and farm laborers. In the state of Vermont the incidence, as might be expected, is excessively high in the granite cutters. In Connecticut, among ax polishers and grinders, the tuberculosis mortality is over ten times that of the state in general. Lime dusts and brick dusts seem harmless, and the same is true of cement dusts and coal dusts—indeed, the latter appears to be beneficial rather than otherwise so far as tuberculosis is concerned.

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